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Karolinska Institutet, Stockholm, Sweden

# **MECHANICAL THROMBECTOMY FOR ACUTE ISCHEMIC STROKE**

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Institutet**

Stockholm 2016

Cover images: Cerebral angiography with selective injection in the right internal carotid artery before and after thrombectomy. The left image demonstrates an occlusion of the middle cerebral artery (MCA) before thrombectomy, and the right image demonstrates complete recanalization with filling of the MCA territory after performed thrombectomy. The patient suffered from left sided hemiplegia and slurred speech, and recovered completely.

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Published by Karolinska Institutet.

Printed by Eprint AB 2016

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ISBN 978-91-7676-458-9

# Mechanical thrombectomy for acute ischemic stroke

## THESIS FOR DOCTORAL DEGREE (Ph.D.)

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***To my beloved family!***



## ABSTRACT

The overall aim of this doctoral thesis was to study the outcome and safety of mechanical thrombectomy, which is an endovascular technique for treating moderate to severe acute ischemic stroke caused by a large cerebral artery occlusion. The technique has been developed over the last two decades. At the onset of this doctoral project, only a limited numbers of studies on the technique had been published, but the results were very promising.

This thesis is based on five peer-reviewed publications. In these studies, it was found that:

- patients with basilar artery occlusions who were treated using mechanical thrombectomy (at Karolinska University Hospital between September 2005 – November 2010), had a significantly better functional outcome compared to patients in other studies, where intravenous thrombolysis or no reperfusion therapy was given (Study I).
- mechanical thrombectomy was a safe and effective method for restoring blood flow in selected patients suffering from a moderate to severe acute ischemic stroke that was caused by a large artery occlusion (Study II). This was concluded from an examination of patients with anterior and posterior circulation strokes who were treated with mechanical thrombectomy at Karolinska University Hospital between September 2005 – December 2011.
- neither prior treatment with intravenous thrombolysis, nor advanced age, was significantly associated with a risk of symptomatic intracranial hemorrhage (Study II).
- functional outcome three months after mechanical thrombectomy was equally good for those over 80 years of age as for those between 50-64 and 65-79 years of age (Study III). This was concluded from an examination of the subgroup of patients from study II with anterior circulation stroke, selected according to practice at Karolinska University Hospital.
- in patients with wake-up stroke, there was no indication of poorer outcome (Study III).
- endovascular treatment combined with intravenous thrombolysis led to a higher ratio of patients with improved functional outcome compared to patients treated with intravenous thrombolysis alone, with an absolute risk reduction of 19% (Study IV). This was concluded from a meta-analysis of six randomized controlled trials.
- the estimated rate of thrombectomy in Sweden in 2013 might have been more than five times higher than the actual rate, if patients had been selected according to our practice at the Karolinska University Hospital (a practice similar to the recently published updated treatment recommendations from both European and American organisations) (Study V). This was concluded by comparing treatment proportions at our institution by level of stroke severity with stroke data from the rest of Sweden, provided from Riksstroke (the Swedish national stroke registry).

In conclusion, it has been shown that mechanical thrombectomy is a safe treatment, which significantly improves the likelihood of functional outcome for patients with moderate to severe stroke. The findings indicate that a substantial increase in demand for this treatment option should be expected. The main challenge now is to fully implement the technique in clinical practice and to be able to offer it to all patients throughout Sweden, not just to those who live in the proximity of a university hospital.

## LIST OF SCIENTIFIC PAPERS

- I. **Mechanical thrombectomy as the primary treatment for acute basilar artery occlusion: experience from 5 years of practice**  
Andersson T, Kuntze Söderqvist Å, Söderman M, Holmin S, Wahlgren N, Kaijser M.  
*Journal of NeuroInterventional Surgery* 2013; 5:221-225, Epub 2012 Mar 20
- II. **Mechanical thrombectomy in acute ischemic stroke - experience from 6 years of practice**  
Kuntze Söderqvist Å, Kaijser M, Söderman M, Holmin S, Wahlgren N, Andersson T.  
*Neuroradiology*, 2014; 56:477–486, Epub 2014 Apr 1
- III. **Mechanical thrombectomy in acute ischemic stroke - wake-up strokes and elderly may benefit as well**  
Kuntze Söderqvist Å, Andersson T, Wahlgren N, Kaijser M.  
*Journal of Stroke and Cerebrovascular Diseases*, Vol. 25, No. 9 (September), 2016: pp 2276–2283, Epub 2016 Jun 6
- IV. **Improved clinical outcome 3 months after endovascular treatment, including thrombectomy, in patients with acute ischemic stroke: a meta-analysis**  
Falk-Delgado A, Kuntze Söderqvist Å, Fransén J, Falk-Delgado A.  
*Journal of NeuroInterventional Surgery* 2016; 8:665-670, Epub 2015 Jul 2
- V. **Thrombectomy in acute ischemic stroke - estimations of increasing demands**  
Kuntze Söderqvist Å, Andersson T, Ahmed N, Wahlgren N, Kaijser M  
*Journal of NeuroInterventional Surgery* 2016; 0:1-4, Epub ahead of print, 2016 Aug 26

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## LIST OF ABBREVIATIONS

ADC	Apparent Diffusion Coefficient
AHA/ASA	American Heart Association/American Stroke Association
AJNR	American Journal of Neuroradiology
ASPECTS	Alberta Stroke Program Early CT Score
ATLANTIS	Alteplase ThromboLysis for Acute Noninterventional Therapy in Ischemic Stroke
ATP	Adenosine TriPhosphate
BASICS	Basilar Artery International Cooperation Study
BCG	Balloon Guide Catheter
BI	Barthel Index
BMM	Best Medical Management
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
CI	Confidence Interval
CT	Computed Tomography
CTP	CT Perfusion
DAWN	Trevo and Medical Management Versus Medical management Alone in Wake Up and Late Presenting Strokes
DWI	Diffusion Weighted Image
EAN	European Academy of Neurology
EANS	European Association of Neurosurgical Societies
ECASS	European Cooperative Acute Stroke Study
EPITHET	Echoplanar Imaging Thrombolytic Evaluation Trial
EROICAS	European Recommendations on Organization of Interventional Care in Acute Stroke
ESCAPE	Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times
ESMINT	European Society of Minimally Invasive Neurological Therapy

ESNR	European Society of Neuroradiology
ESO	European Stroke Organisation
EU	European Union
EuSEM	European Society of Emergency Medicine
EVAS	EndoVaskulär behandling av Akut Stroke
EXTAND IA	Extending the Time for Thrombolysis in Emergency Neurological Deficits – Intra-Arterial
GCS	Glasgow Coma Scale
HERMES	Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials
HU	Hounsfield Units
IAT	Intra Arterial Thrombolysis
ICA	Internal Carotid Artery
IMS	Interventional Management of Stroke
IVT	IntraVenous Thrombolysis
JAMA	Journal of the American Medical Association
LOC	Level of Consciousness
MCA	Middle Cerebral Artery
MELT	Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial
MERCI	Mechanical Embolus Removal in Cerebral Ischemia
MR	Magnetic Resonance Imaging
MR CLEAN	Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands
MR RESCUE	Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy
MRI	Magnetic Resonance Imaging
mRS	modified Rankin Scale
mTICI	modified Treatment In Cerebral Ischemia
mTICI	modified Thrombolysis in Cerebral Infarction
MTT	Mean Transit Time



M1, M2, M3 etc	Segments of MCA, M1 most proximal, M2 the next etc.
NEJM	New England Journal of Medicine
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
NNT	Number Needed to Treat
OR	Odds Ratio
PROACT	Prolyse in Acute Cerebral Thromboembolism
REVASCAT	Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset
rt-PA	recombinant tissue Plasminogen Activator
SICH	Symptomatic IntraCranial Hemorrhage
SITS	Safe Implementation of Thrombolysis in Stroke
SITS-ISTR	SITS-International Stroke Treatment Registry
SITS-MOST	SITS–Monitoring Study
SWIFT	The Solitaire With the Intention For Thrombectomy
SWIFT PRIME	The Solitaire With the Intention For Thrombectomy as Primary Endovascular Treatment
SYNTHESIS	Local versus Systemic Thrombolysis for Acute Ischemic Stroke
THERAPY	The Randomized, Concurrent Controlled Trial to Assess the Penumbra System’s Safety and Effectiveness in the Treatment of Acute Stroke
TICI	Thrombolysis In Cerebral Infarction
TIMI	Thrombolysis In Myocardial Infarction
TLV	Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket)
tPA	tissue Plasminogen Activator
THRACE	THRombectomy des Artères Cerebrales
TREVO	Thrombectomy REvascularization of large Vessel Occlusions in acute ischemic stroke

TTP	Time To Peak
UK-TIA	United Kingdom Transient Ischaemic Attack
USA	United States of America
VISTA	Virtual International Stroke Trials Archive

# 1 INTRODUCTION

Mechanical thrombectomy is an endovascular technique to treat moderate to severe acute ischemic stroke, when a large artery in the brain is occluded. This technique has been developed during the last two decades. At the beginning of this doctoral project there were only a limited numbers of studies published about the clinical outcome of this technique, although with very promising results. The department of neuroradiology at the Karolinska University Hospital adopted the method quite early and the first thrombectomy was performed in September 2005. This doctoral project started in June 2010 and by that time the department had one of the largest series of performed thrombectomies in Europe. The main aim of this doctoral project was to further examine the safety and effectiveness of the method.

## **2 BACKGROUND**

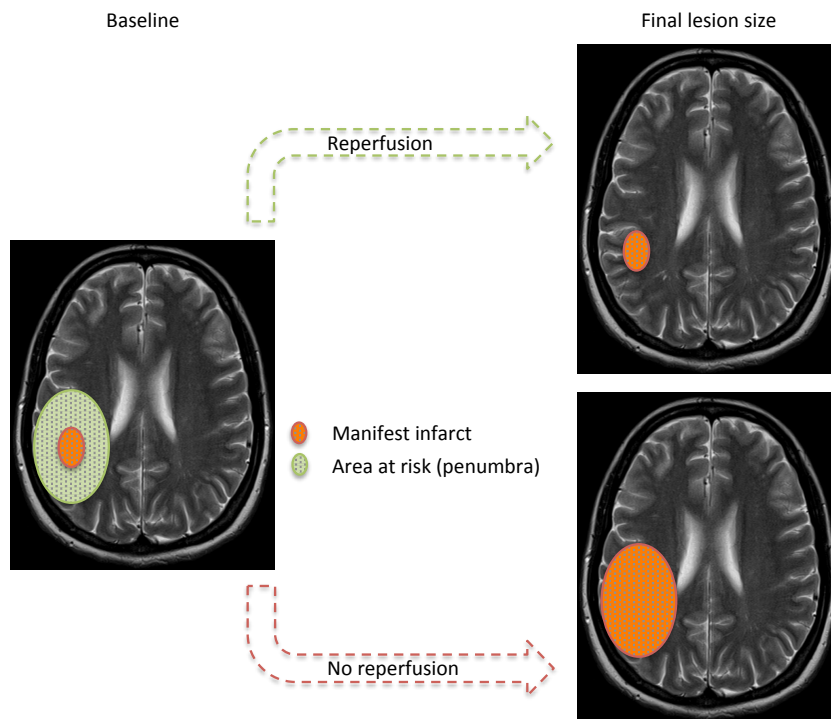
### **2.1 WHAT IS STROKE?**

Acute stroke is today the second leading cause of death in the world, responsible for 11% of overall mortality.<sup>1,2</sup> A stroke occurs either when the blood flow to an area in the brain is obstructed by a blood clot in a blood vessel (ischemic stroke) or when a blood vessel ruptures in the brain or at the brain's surface (hemorrhagic stroke). About 85% of all strokes are ischemic and the remainder are hemorrhagic.<sup>3</sup> In Sweden, about 25 000 people suffer from acute stroke every year, with the mean age for stroke approximately 76 years (73 years for men and 78 years for women).<sup>4</sup> In addition to human suffering, the economic burden for treatment and rehabilitation for these patients is obviously very large.

In this thesis only ischemic stroke is addressed.

#### **2.1.1 Pathophysiology**

When a cerebral artery is occluded, within seconds the cells in the territory supplied by that vessel lose basic function such as synaptic transmission, ion pumping and energy metabolism, eventually leading to cellular necrosis. The damage is caused by activation of the ischemic cascade, which progresses to total depletion of oxygen or glucose, causing failure of high energy phosphate compounds like adenosine triphosphate (ATP). This affects energy-dependent processes necessary for tissue cell survival, and sets off a series of interrelated events culminating in cellular injury and death.<sup>5</sup> However, total loss of function and subsequent development of infarction only occur if the ischemia is complete. If residual perfusion persists, due to for example additional blood supply from collateral vessels, an area of perfused brain tissue with electrical failure but sustained energy metabolism and normal extracellular potassium levels may develop. Astrup et al. described this, in 1981, as ischemic penumbra.<sup>6</sup> In this "tissue at risk" the perfusion restriction is thought to be severe enough to arrest physiological function, but not so complete as to cause irreversible infarction.<sup>7-9</sup> If revascularisation occurs in time, this penumbral area might regain its function. The concept of reversibility encouraged the search for both ways to image the potentially salvageable brain tissue<sup>10</sup> and for reperfusion treatments.



**Figure 1.** Penumbra. At baseline a small infarct core is already manifest, and a larger surrounding area is at risk (penumbra). If reperfusion is achieved in time, the tissue at risk can be salvaged. If not, the final manifest infarct will also include the penumbra.

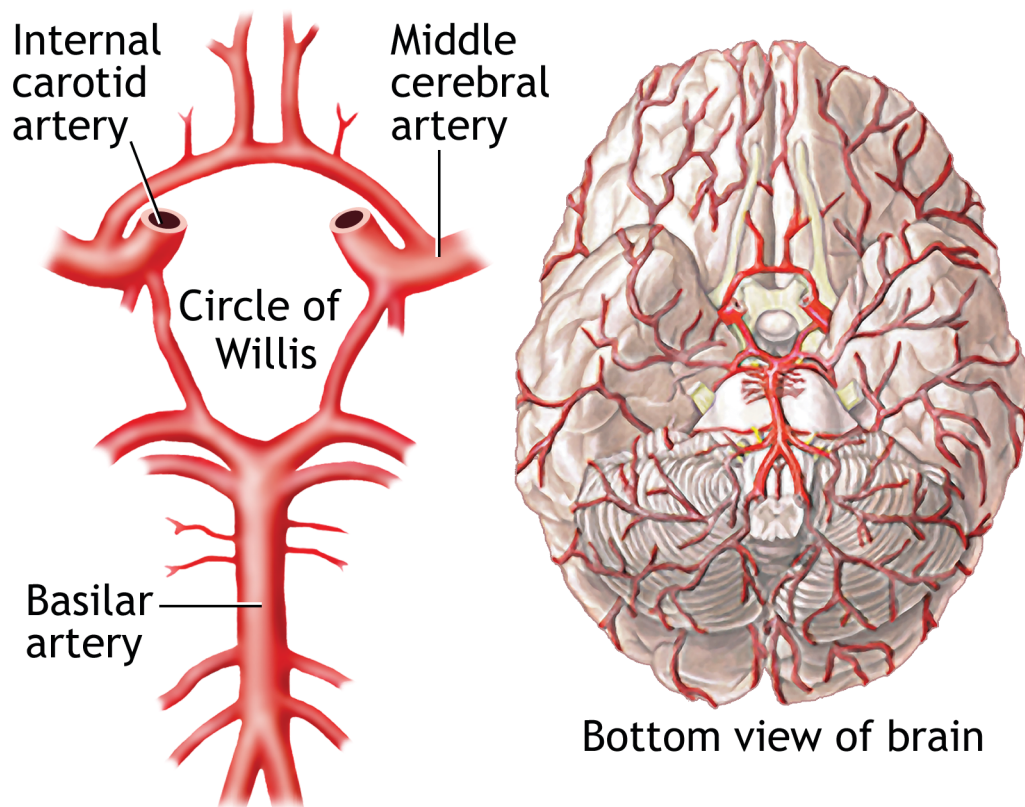
### 2.1.2 Time and collaterals

For the stroke population in general, time to reperfusion is of utmost importance.<sup>11-14</sup> For the specific patient there might be other factors that are as crucial. There is a huge inter-individual difference in how fast an infarct develops; one patient with an M1-occlusion might have a manifest infarct in the entire middle cerebral artery territory after less than one hour and another patient, with a similar occlusion, might have salvageable tissue after six or even eight hours.<sup>15</sup> Collaterals, which are alternative ways for blood to reach the target tissue, are of great importance.<sup>16</sup> Many additional, as yet unknown factors will likely be discovered.

#### 2.1.2.1 Circle of Willis

The blood vessels for both the left and right hemispheres originating from the internal carotid arteries (the anterior circulation) and the blood vessels originating from the vertebrobasilar system (the posterior circulation) are connected at the skull base through the circle of Willis.<sup>17</sup> This circle forms a collateral system and is complete in only 40-50% of all

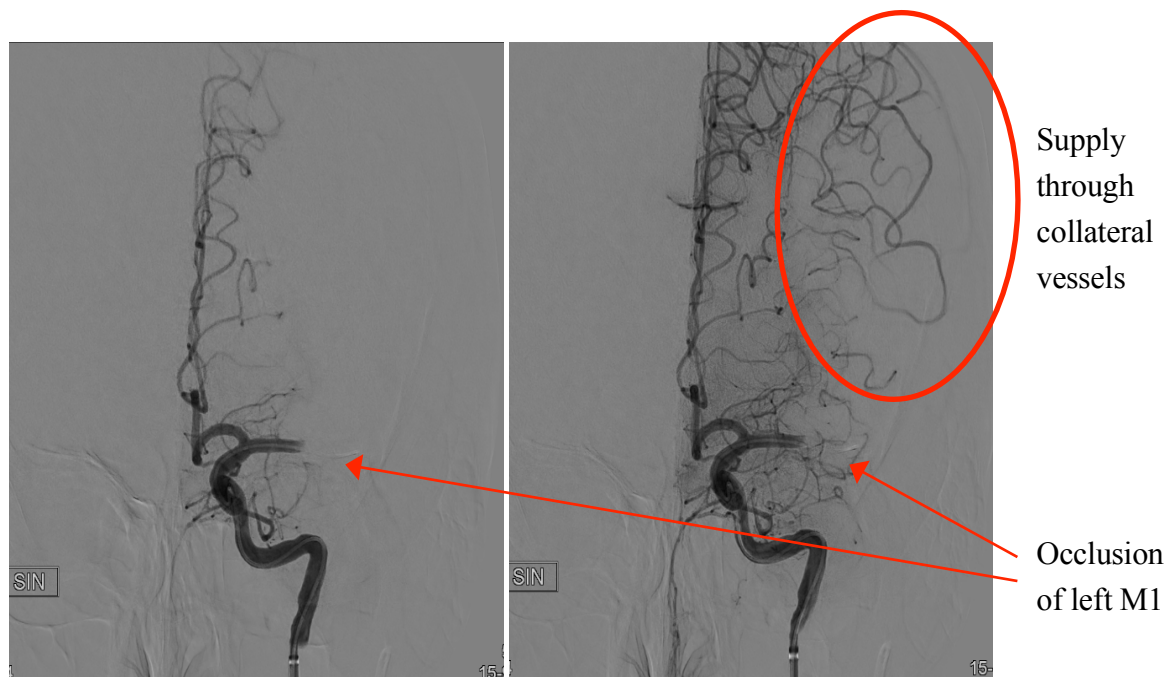
patients.<sup>18</sup> This collateral system only helps with an occlusion proximal to the circle. In the anterior circulation this would be in the internal carotid artery proximal to the origin of the posterior communicating artery and in the posterior circulation in or proximal to the P1 segment of the posterior cerebral artery.



**Figure 2.** Circle of Willis. (Image reprinted with permission from A.D.A.M.)

#### 2.1.2.2 Pial collaterals

There exists a leptomeningeal (pial) collateral network, over the surface of the brain, which allows the anterior and posterior cerebral arteries to provide additional blood supply to at least part of the territory of the middle cerebral artery (MCA) in case of an MCA-occlusion, and vice versa.<sup>19</sup> These collateral vessels widely differ in width and number between different individuals, and may also develop over time, for example in the case of an intracerebral stenosis that reduces flow in one territory.<sup>20</sup>



**Figure 3.** Pial collaterals. Carotid artery angiogram in frontal projection. The image on the right is taken 2 seconds after the image to the left. Note late filling through collateral vessels from the anterior cerebral artery to the area usually supplied by the middle cerebral artery.

#### 2.1.2.3 Dural-pial collaterals

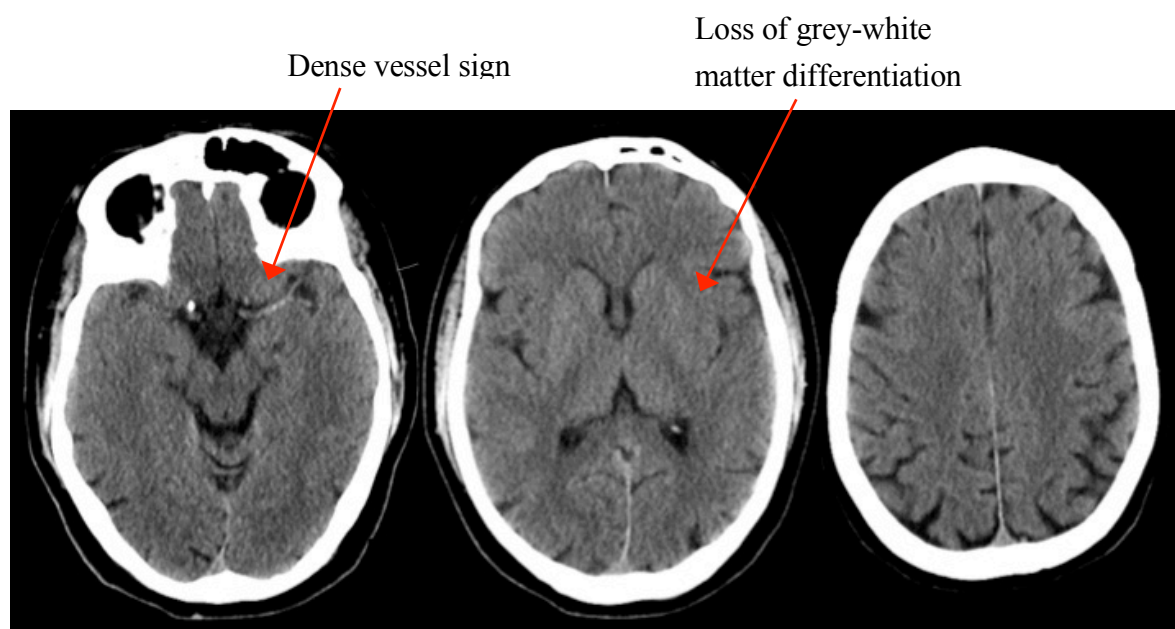
The external system, most notably the external carotid arteries, supplies blood to dural (meningeal) and extra cerebral structures. The internal system, the branches called pial vessels, originating from the internal carotid and the vertebrobasilar arteries, supplies the brain parenchyma. There are several connections between the external and the internal systems; one of the most common, seen in cases of stenosis or occlusion of the internal carotid artery, is a connection via the ophthalmic artery.<sup>17</sup> These connections exist mostly in the base of the skull, and therefore only help in cases of proximal occlusion or stenosis.

## 2.2 IMAGING OF STROKE

Since there are no physiologic or blood biomarkers for stroke, imaging has evolved as the best available method for detection of acute stroke. Many of the advances that have been made in the treatment of acute stroke during the last three decades would never have been feasible without the advances in neuroimaging. Initially imaging was used merely to exclude hemorrhage, in order to determine whether to give intravenous thrombolysis (IVT) or not. More recently, imaging is used to try to comprehend and demonstrate the pathophysiology behind the acute stroke. In the acute setting, the role of neuroimaging has become to provide fast critical diagnostic information that will determine the acute treatment decisions.

### 2.2.1 Computed tomography

In the 1990s computed tomography (CT) made it possible to see early signs of cerebral infarction, as early as a few hours after onset of symptoms. Since then the technique has developed remarkably, and today early signs can often be detected with CT within an hour. The main use of unenhanced CT is to exclude hemorrhage before IVT can be given, but also to exclude the presence of large manifest infarcts. Signs of early infarction may be hypoattenuation, loss of grey-white matter differentiation and localized mass effect, as can be observed by so-called sulcal effacement. Sometimes the actual thrombus can be observed as a high attenuating structure, as the “dense vessel sign”. These early signs can be difficult to detect and there is an interobserver variability, where experience has been shown to improve detection.<sup>21</sup>



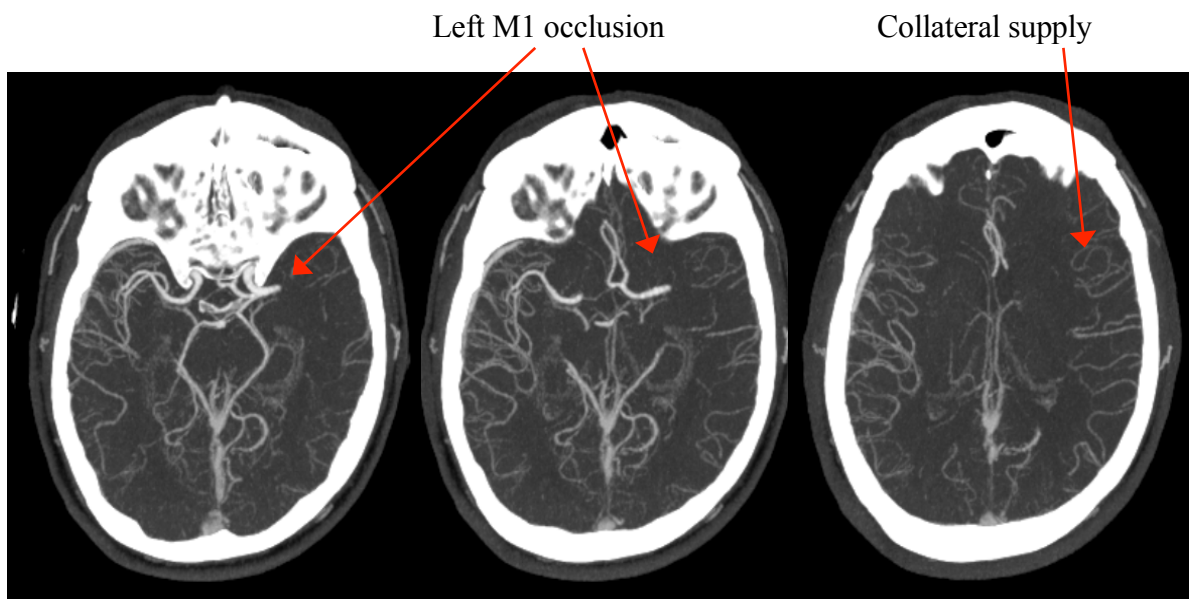
**Figure 4.** Axial CT images of the brain. Note dense vessel sign of the left middle cerebral artery (left image) and the loss of grey-white matter differentiation around the left putamen (middle image). No signs of infarction in the right image.

### 2.2.2 CT-angiography

If CT-imaging is performed during administration of intravenous contrast media, the cerebral vascular anatomy can be studied. Intravenous contrast is administered by a power injector, followed by a saline-injection at the same rate to rapidly push all the contrast into the vascular system. Scanning is performed at a single time point after contrast injection, making it a



“snapshot” of the enhanced cerebrovascular anatomy.<sup>22</sup> Depending of the timing of the acquisition either the arteries or the veins will be visualized best. Due to advances in technology, scanning from the aortic arch to the vertex can be completed with a single contrast injection in only a few seconds. The great advantage of this technique is the ability to evaluate not only the location of an intracerebral occlusion, but also to evaluate the aortic arch and cervical vessels in order to diagnose extracranial atherosclerosis, stenoses or dissections as well as to plan the interventional procedure. The ability to visualize the occlusion site enabled the increasing use of mechanical thrombectomy.



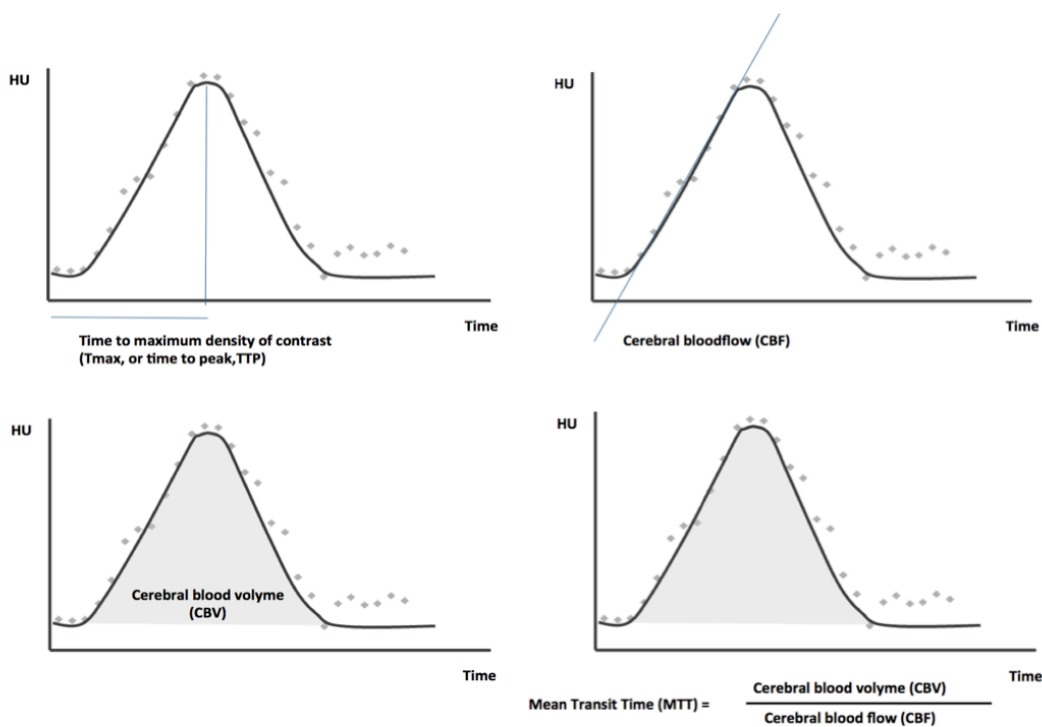
**Figure 5.** CT angiography. Occlusion of the left middle cerebral artery (right side in each image). The arteries in the left hemisphere, seen beyond the occlusion, are supplied in retrograde direction via the anterior and posterior cerebral arteries (collateral flow).

### 2.2.3 Multiphase CT

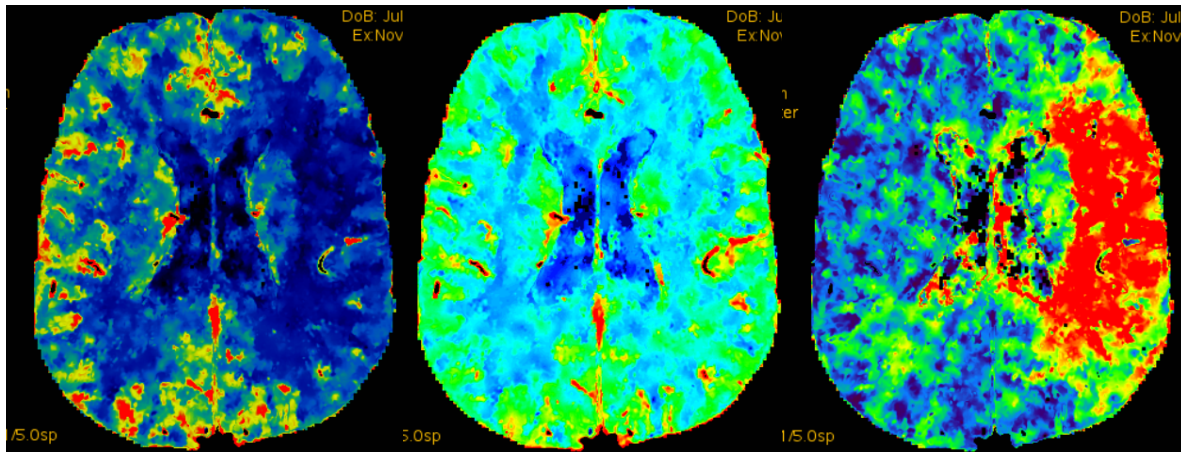
As multidetector CT scanners increased scanning speed in the late 1990s different techniques were developed by repeating serial static mode acquisitions during a single contrast injection. This has made it possible to scan, for example, first in arterial phase then in venous phase and finally in late venous phase.<sup>23</sup> Multiphase CT makes it possible to evaluate the status of collateral circulation, and might help in selecting patients for thrombectomy and in prediction of outcome.<sup>23</sup>

## 2.2.4 CT perfusion

Continuous scanning mode is a way to further improve the temporal information, by repeatedly scanning the targeted region.<sup>22</sup> To minimize the higher radiation dose as a result of increased scanning, different post-processing techniques were developed. Cerebral perfusion can be described by several parameters, of which some are more commonly used. Cerebral Blood Flow, CBF, is defined as the volume of blood moving through a given volume of brain per unit time, measured in millilitres of blood per 100g of brain tissue per minute. Cerebral Blood Volume, CBV, is defined as the total volume of flowing blood present in a given volume in the brain, measured in millilitres of blood per 100 g of brain tissue. Mean Transit Time, MTT, is the average transit time of blood through a given brain region, and Time To Peak, TTP, describes the time required to achieve maximum density of contrast within a specific region of brain tissue, both measured in seconds.<sup>22,24</sup> Differentiation between the infarcted tissue and the penumbra is based on the concept of cerebral vascular autoregulation. Infarcted tissue loses its ability to autoregulate, which manifests as matched reduction in CBF and CBV with prolonged MTT. On the other hand, penumbra maintains its ability to autoregulate, thus CBV is sustained with prolonged MTT.<sup>25,26</sup> It has been difficult to establish a robust absolute definition of infarct core and penumbra, and several have been suggested - absolute CBV,<sup>25</sup> the product of absolute CBV and CBF,<sup>27</sup> and relative CBF.<sup>28</sup> CT perfusion is also used for selection of patients for thrombectomy and prediction of outcome.



**Figure 6.** CT perfusion, attenuation of contrast medium measured in Hounsfield Units (HU) plotted against time, describing the different parameters used. (*Courtesy of M Kaijser.*)

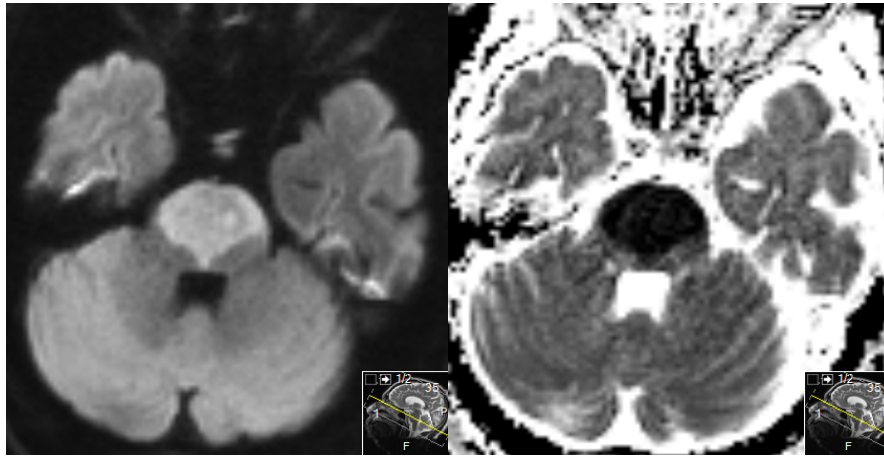


**Figure 7.** CT perfusion images. Cerebral Blood Flow (CBF) to the left, Cerebral Blood Volume (CBV) in the middle, Mean Transit Time (MTT) to the right, all from the same axial slice in the same patient. Colour coded scales are not shown in the figure: the two hemispheres can be compared with each other. A perfusion defect is seen in the left hemisphere (right side on the images), with reduction of CBF and prolonged MTT, but with maintained CBV (penumbra).

### 2.2.5 Magnetic Resonance Imaging

Although many centres prefer CT in stroke evaluation, due to the speed and availability, others prefer magnetic resonance imaging (MRI) due to its superior ability to assess the infarct core with diffusion sequences.<sup>29,30</sup> One disadvantage with MRI is that it may be time consuming. Even if the actual scanning time can be reduced, it often takes time to get the patient into the scanner. Contraindications for MRI, such as pacemaker or other metal objects, must be assessed. If the patient has difficulties in understanding instructions and to remain still it may be difficult to obtain high quality images, since they usually are acquired over several minutes. In such cases sedation or general anaesthesia may be needed, which also adds extra time and risk. One situation where MR is an especially valuable tool is in posterior circulation strokes, since it may be difficult to evaluate ischemic changes in the brainstem on CT.

The type of imaging (CT or MRI) used in the work up of stroke in practice may be most dependent on local organizational factors and availability.<sup>31</sup>



**Figure 8.** MRI at the level of pons and cerebellum. Diffusion Weighted Image (DWI) in the left image and Apparent Diffusion Coefficient (ADC) in the right image, demonstrating an area of restricted diffusion, as in a large infarction, in the pons.

## 2.3 BASELINE AND OUTCOME MEASUREMENTS

There are several ways to measure severity as well as short and long term outcomes of stroke. A variety of rating scores are commonly used. In this section a selection will be described.

### 2.3.1 Stroke severity

A widely used scale for assessing stroke severity is the National Institutes of Health Stroke Scale (NIHSS) score.<sup>32,33</sup> Points are given for level of consciousness, orientation, ability to obey command, gaze problems, visual loss, facial palsy, motor function in arm and leg, limb ataxia, sensory loss, dysphasia, dysarthria, and neglect etc. (figure 9). The score correlates best to the severity of stroke in the anterior circulation. Stroke in the posterior circulation can be severe without effect on NIHSS score.<sup>34</sup> The currently NIHSS is composed of eleven main items and it ranges from 0 to 42, in which 0 means absence of neurological symptom and 42 corresponds to maximum severity.

The Glasgow Coma Scale (GCS) was described in 1974, as a way to describe the level of consciousness of patients with an acute brain injury.<sup>35,36</sup> The scale is divided in three parts testing eye opening, verbal response and motor response, with a minimum of 3 points (coma) and a maximum of 15 points (normal status, alert) (figure 10). The GCS may be useful, especially for patients with posterior circulation stroke in which varying levels of consciousness is among the potential symptoms.<sup>37</sup>

The National Institutes of Health Stroke Scale			
Category	Score/Description	Score	
<b>1a. Level of Consciousness</b>	0 = Alert; keenly responsive 1 = Arouses to minor stimulation 2 = Requires repeated stimulation to arouse 3 = Unresponsive, coma		
<b>1b. LOC Questions</b> (Month, age)	0 = Answers both correctly 1 = Answers one correctly 2 = Incorrect		
<b>1b. LOC Commands</b> (Open/close eyes, squeeze hands)	0 = Obeys both correctly 1 = Obeys one correctly 2 = Incorrect		
<b>2. Best Gaze</b> (Eyes open – patient follows examiner’s finger or face)	0 = Normal 1 = Partial Gaze Palsy 2 = Forced deviation		
<b>3. Visual Fields</b> (Introduce visual stimulus/threat to patients visual field quadrants)	0 = No visual loss 1 = Partial Hemianopia 2 = Complete Hemianopia 3 = Bilateral Hemianopia (Blind)		
<b>4. Facial Paresis</b> (Show teeth, raise eyebrows and squeeze eyes shut)	0 = Normal 1 = Minor 2 = Partial 3 = Complete		
<b>5a Motor Arm – Left</b> <b>5b Motor Arm – Right</b> (Elevate arm to 90° if patient is sitting, 45° if supine)	0 = No drift 1 = Drift 2 = Can’t resist gravity 3 = No effort against gravity 4 = No movement x = Untestable (joint fusion or amputation)	Left	
		Right	
<b>6a Motor Leg – Left</b> <b>6b Motor Leg– Right</b> (Elevate leg 30° with patient supine)	0 = No drift 1 = Drift 2 = Can’t resist gravity 3 = No effort against gravity 4 = No movement x = Untestable (joint fusion or amputation)	Left	
		Right	
<b>7. Limp ataxia</b> (Finger-nose, heel down shin)	0 = No ataxia 1 = Present in one limb 2 = Present in two limbs		
<b>8. Sensory</b> (Pin prick to face, arm, trunk and leg – compare sides)	0 = Normal 1 = Partial Loss 2 = Severe loss		
<b>9. Best language</b> (Name items, describe a picture and read a sentence)	0 = No aphasia 1 = Mild to moderate aphasia 2 = Severe aphasia 3 = Mute		
<b>10. Dysarthria</b> (Evaluate speech clarity by patient repeating listed words)	0 = Normal articulation 1 = Mild to moderate alluring of words 2 = Near to unintelligible or worse x = Intubated or other physical barrier		
<b>11. Extinction and Inattention</b> (Use information from prior testing to identify neglect or double simultaneous stimuli testing)	0 = No neglect 1 = Partial neglect 2 = Complete neglect		

**Figure 9.** The National Institutes of Health Stroke Scale, NIHSS. *(Image created by the author of this thesis)*

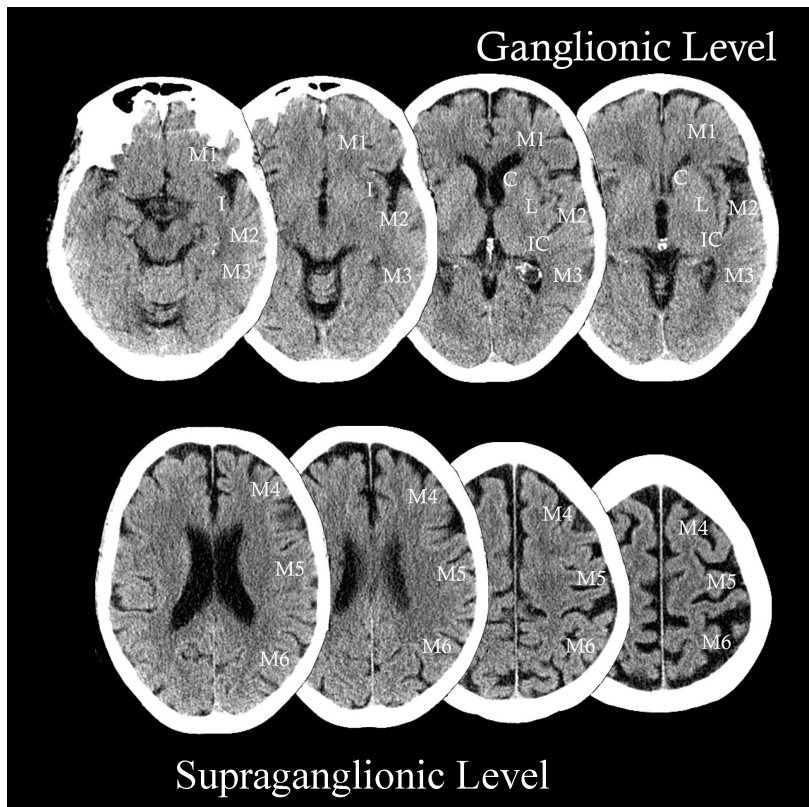
Glasgow Coma Scale		
Category	Score/Description	Score
Best eye response (E)	1 = None 2 = To pressure 3 = To speech 4 = Spontaneous	
Best verbal response (V)	1 = None 2 = Sounds 3 = Words 4 = Confused 5 = Oriented	
Best motor response (M)	1 = None 2 = Extension 3 = Abnormal flexion 4 = Normal flexion (withdrawal) 5 = Localising 6 = Obeying commands	

**Figure 10.** Glasgow Coma Scale, GCS.<sup>36</sup> *(Image created by the author of this thesis)*

### 2.3.2 Size of early ischemic lesion/manifest infarct

In the European Cooperative Acute Stroke Study (ECASS) trial patients were excluded from IVT if early ischemic findings exceeded one third of the MCA territory.<sup>38,39</sup> Unfortunately, later research has shown that even experienced radiologists and stroke physicians have difficulties both to correctly interpret early ischemic lesions on CT and to quantify them reliably.<sup>21,40-42</sup> In order to create a more reliable and reproducible grading system, the Alberta Stroke Program Early CT Score (ASPECTS) was suggested by Pexman et al. in 2001.<sup>43</sup> ASPECTS is a 10-point scale that rates the presence or absence of ischemia in 10 regions of the middle cerebral artery territory (figure 11). A normal CT scan receives an ASPECTS of 10 points; a single point is subtracted for every area with early ischemic change, visualized as focal swelling or parenchymal hypoattenuation.

ASPECTS can be applied both before and after reperfusion therapy, in order to evaluate tissue outcome.



**Figure 11.** The ten included areas of ASPECTS. C – Caudate nucleus, L - Lentiform nucleus, IC - Internal Capsule, I – Insular cortex, M1, M2, M3 - middle cerebral artery territory at the level of the basal ganglia, M4, M5, and M6 - middle cerebral artery territory at the level of cella media and above. (*Image reprinted with permission from aspectsinstroke.com*)

### 2.3.3 Reperfusion

Technical results after thrombectomy are most often rated by a grading score of reperfusion or revascularization as seen on cerebral angiography. At first a scale adopted from coronary angiography, the Thrombolysis In Myocardial Infarction (TIMI) scale, or variants thereof, was used.<sup>44</sup> Later, the TIMI scale was transformed into the Thrombolysis in Cerebral Infarction (TICI) scale, adapted to the cerebral circulation,<sup>45</sup> further modified into the modified TICI (mTICI) scale<sup>46</sup> by the Interventional Management of Stroke (IMS) study investigators. The mTICI scale differs from the TICI scale in the definition of the score 2a and 2b, where the modified scale uses perfusion of less than or more than 50% of the MCA-territory and the TICI scale has less than or more than 2/3 as a cut off. Later, an extra sub classification 2c was added.<sup>47</sup> The different scales make it difficult to compare studies, and Zaidat et al made an attempt to uniform the grading in 2013, in which they recommended the use of mTICI (grade 0, 1, 2a, 2b and 3), but changed the meaning of the acronym to modified Treatment In Cerebral Ischemia, acknowledging that treatment consists not only of thrombolysis (figure 12).<sup>48</sup>

Modified Treatment in Cerebral Ischemic Scale	
Score	Definitions
0	No perfusion
1	Antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion.
2a	Antegrade reperfusion of less than half of the occluded target artery previously ischemic territory (e.g., in 1 major division of the MCA and its territory)
2b	Antegrade reperfusion of more than half of the previously occluded target artery ischemic territory (e.g., in 2 major division of the MCA and their territories)
3	Complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches.

**Figure 12.** Modified Treatment in Cerebral Ischemia Scale, mTICI.<sup>48</sup> *(Image created by the author of this thesis)*

### 2.3.4 Functional outcome

The modified Rankin Scale (mRS) is a commonly used scale for measuring the degree of disability in the daily activities of people who have suffered from a stroke, in most studies evaluated after 3 months. The scale was originally introduced in 1957 by Dr John Rankin from Glasgow, Scotland,<sup>49</sup> and later modified for use in the United Kingdom transient ischaemic attack (UK-TIA) trial in the late 1980s (figure 13).<sup>50</sup> This scale can be used in several different ways, either dichotomised in different cut-off level groupings such as mRS 0-1 representing excellent outcome, mRS 0-2 representing good outcome or functional independence, or mRS 5-6 as poor outcome, compared to the rest of the scores in the scale (mRS 2-6, mRS 3-6 and mRS 0-4 respectively). The mRS can also be used in shift analysis, in which a shift towards better or worse outcome across the scale is compared between the studied groups.<sup>51</sup> An advantage of shift analysis is the ability to detect shifts or changes in the middle of the mRS spectrum, which might be clinically meaningful.



The modified Rankin Scale, mRS	
Score	Definition
0	No Symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderately severe disability. Unable to attend to own bodily needs without assistance or unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden.
6	Dead

**Figure 13.** The modified Rankin Scale, mRS. *(Image created by the author of this thesis)*

Another commonly used scale measuring functional outcome is the Barthel index (BI), developed in 1965 and modified by Granger et al. in 1979.<sup>52</sup> BI measures the patient's performance in ten activities of daily living (feeding, grooming, bathing, dressing, bowel and bladder care, toilet use, ambulation, transfers, and stair climbing), with a maximum score of 100. The lowest score is 0, representing a totally bedridden state. The BI measures performance of specific tasks, rather than independence – as measured by the mRS. Both scales are easy to use, have acceptable degree of reliability, and both have been used in several studies.<sup>52</sup>

There are several other scales measuring outcome after stroke, but in our studies we chose to use only the mRS scale.

### 2.3.5 Symptomatic intracranial hemorrhage

Asymptomatic hemorrhagic transformation, usually small petechiae at the edges of the infarct or within the infarcted area, is often seen when successful recanalization has occurred and is thought to be without clinical impact.<sup>53</sup> When a hemorrhage causes clinical deterioration, it is classified as symptomatic intracranial hemorrhage (SICH), which is the most common reported severe adverse event. In our studies we have reported SICH according to the SITS-MOST (Safe Implementation of Thrombolysis in Stroke–Monitoring Study) definition: an intracerebral hemorrhage exceeding 30% of the infarcted volume with significant space occupying effect on the post-treatment imaging scan leading to a decline in NIHSS score of

$\geq 4$  points or causing death within 36 h.<sup>54</sup> There are several other definitions used in different trials, which makes comparison between studies more difficult. In the National Institute of Neurological Disorders and Stroke (NINDS) trial any CT-documented hemorrhage that was temporally (within the first 36h) related to any decline in the patients neurological status, judged by the clinical investigator, was defined as SICH.<sup>55</sup> In PROACT (Prolyse in Acute Cerebral Thromboembolism) II the definition was hemorrhagic transformation within 24 hours causing a decline in NIHSS score of  $\geq 4$  points or a 1-point deterioration in level of consciousness.<sup>56</sup> In ECASS III any apparently extravascular blood within the cranium identified as the predominant cause of neurological deterioration (defined as a decline in NIHSS score of  $\geq 4$  points or leading to death) was regarded as SICH.<sup>57</sup>

### **2.3.6 Mortality**

The proportion of deaths during a specified time period, case fatality rate, is the most commonly used measurement. Most publications use the number of deaths at 3 months after treatment. Since most authors include all deaths during this time period, not only those caused by stroke, we chose to do the same.

## **2.4 TREATMENT OF STROKE**

Since time immemorial stroke has been a devastating disease, with little to do but to accept and to make the most of whatever function is remaining. Fortunately, much progress has been made during the last four decades, and up till the present time three eras in the evolution of modern ischemic stroke care can be discerned. The first era was characterised by stroke specific care and the development of specialized stroke units. Next came the era of intravenous thrombolysis, and most recently the era of endovascular mechanical thrombectomy.

### **2.4.1 Specialized stroke units**

In the 1980-1990s several studies comparing specialized stroke units with general medical wards were published.<sup>58-61</sup> Stroke units emphasized the value of a team approach to nursing and rehabilitation and the importance of starting rehabilitation early. Stroke unit treatment was shown to reduce the length of hospital stay, reduce the need for institutional care and in some of the studies also to decrease in mortality rates.<sup>61</sup> The beneficial effect of stroke unit care has been confirmed in several studies.<sup>62,63</sup> The convergence of multidisciplinary treatment, monitoring and care in dedicated stroke units prevents complications, improves functional outcomes and reduces stroke mortality.

## 2.4.2 Intravenous thrombolysis

Intravenous thrombolytic drugs were first used in the late 1950s for acute stroke.<sup>64</sup> Up to the early 1990s several case series, open trials and some randomized trials were performed, most of which were small with heterogeneous inclusion criteria and treatment. Therefore there were no clear evidence of either positive or negative effects of intravenous thrombolysis, and there was a fear of hemorrhagic transformation.<sup>65</sup> It was not until the second half of the 1990s that the new treatment gained more widespread interest.

### 2.4.2.1 Randomized trials in the 1990s

There were several randomized controlled studies conducted during the 1990s, involving streptokinase and alteplase (tissue plasminogen activator, tPA). Results from randomized trials of intravenous treatment with streptokinase were nonfavourable, including an increase in mortality.<sup>66,67</sup> Results with alteplase were mixed,<sup>38,39,55,68,69</sup> but overall showed a time-dependent benefit.<sup>70,71</sup>

In 1995, Hacke et al. published “Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS)” in the Journal of the American Medical Association (JAMA).<sup>38</sup> The study was randomized and included 640 patients from 14 different European countries demonstrating that in a selected population, including patients with moderate to severe neurologic deficit and without extended infarct signs on the initial CT scan, treatment with alteplase within six hours from stroke onset could improve outcome. Reassuringly they did not find any statistically significant differences in the mortality rate at 30 days or in the overall incidence of intracerebral hemorrhages. However, the occurrence of large parenchymal hemorrhages was significantly more frequent in the group treated with alteplase.

The same year, New England Journal of Medicine (NEJM) published the results from another randomized trial, “Tissue plasminogen activator for acute ischemic stroke”, performed by the NINDS rt-PA Stroke Study Group.<sup>55</sup> This study assessed the efficacy and safety of rt-PA when given within three hours from stroke onset, using a lower dose of alteplase than was used in the ECASS study (0.9 mg/kg bodyweight instead of 1.1 mg/kg). Despite an increased incidence of symptomatic intracerebral hemorrhage, patients receiving rt-PA were at least 30% more likely to have minimal or no disability at 3 months than those who received placebo.

On the basis of the NINDS-study, alteplase was approved in the United States of America (USA) for use within three hours of onset of symptoms.<sup>39</sup>

In 1998, results were published from a new randomized trial, ECASS II, in which patients were treated with the same dose of alteplase as used in the NINDS-trial, but with a time-

window of 6 h. In this study patients with signs of early infarct involving more than one third of the middle cerebral artery territory were excluded.<sup>39</sup> The study did not confirm a statistical benefit for alteplase when mRS 0-1 was regarded as favourable outcome. Still, the authors (Hacke et al.) believed that the trend they found towards efficacy should be interpreted in the light of evidence from previous trials. A post-hoc analysis was also performed, in which mRS 0-2 was used as end-point (not predefined), and then there was a statistically significant 8.3% absolute difference in favour of alteplase. Despite the increased risk of intracranial hemorrhage the authors proposed that thrombolysis with alteplase at a dose of 0.9 mg/kg in selected patients could lead to a clinically relevant improvement in outcome.

A year later data from the Alteplase ThromboLysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) part B was published, failing to find a treatment benefit for tPA given 3 to 5 hours after symptom onset.<sup>68</sup> In 2002 results from treatment within 3 hours were published, supporting the recommendation for early treatment since those patients had a more favourable outcome.<sup>69</sup>

#### *2.4.2.2 Consequences*

During this time period stroke care underwent a transformation. Prior to this, acute stroke patients were mostly just observed and provided supportive measures, but now acute treatment and the idea of “time is brain” came into focus. Alteplase was licensed for the treatment of acute ischemic stroke in the USA in 1996, and in Canada in 1999, for selected patients treated within 3 h of symptom onset. In the European Union (EU), a licence was granted in 2002 on two conditions: the establishment of an observational safety study, the Safe Implementation of Thrombolysis in Stroke–Monitoring Study (SITS-MOST) to assess the safety profile of alteplase in routine clinical practice within 3 h of the onset of stroke symptoms,<sup>54</sup> and the initiation of a new randomised trial, the European Cooperative Acute Stroke Study (ECASS) III, with a therapeutic window extended beyond 3 h.<sup>57</sup> The results of both studies were to serve as a basis for the reassessment of the benefit/risk profile of alteplase for the thrombolytic treatment of acute ischemic stroke in the EU.

In Sweden in 2005, only 3,3% of all stroke patients were given IVT according to the annual report from the Swedish National Stroke Register (Riksstroke).<sup>72</sup>

#### *2.4.2.3 Confirmation*

In 2007, results from SITS-MOST, an observational study with 6483 patients from 285 centres in 14 countries, confirmed that intravenous alteplase was safe and effective in routine clinical use when used within 3 h of stroke onset.<sup>54</sup>

#### *2.4.2.4 Time-window*

In 2004, a pooled analysis of ATLANTIS, ECASS AND NINDS rt-PA stroke trials confirmed the association between rapid treatment with intravenous thrombolysis and favourable outcome, and suggested a potential benefit up to 4.5 h after symptom onset, although not as effective as early treatment, up to three hours.<sup>70</sup>

In 2008, ECASS III (a double-blind, parallel-group trial that enrolled patients from multiple centres across Europe) showed that intravenous alteplase administered between 3 and 4.5 hours after the onset of symptoms significantly improved clinical outcomes in patients with acute ischemic stroke, but that alteplase was more frequently associated with symptomatic intracranial hemorrhage.<sup>57</sup>

The same year, additional results from the observational study SITS-ISTR (SITS-International Stroke Treatment Registry) demonstrated that alteplase remained safe when given at 3-4.5 h after ischemic stroke.<sup>73</sup>

In 2010 Lee et al. made an updated pooled analysis of ECASS, ATLANTIS, NINDS, and Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) trials and concluded that patients with ischemic stroke selected by clinical symptoms and CT benefit from intravenous alteplase when treated up to 4.5 h.<sup>11</sup> For maximal benefit every effort should be taken to shorten delay in initiation of treatment; beyond 4.5 h, risk might outweigh benefit. They found that depending on the time of onset 5-15 patients have to be treated in order to have an excellent outcome for one individual. In 2012, Wardlaw et al. performed a systematic review and meta-analysis of 12 randomized trials, supporting the evidence that some patients might benefit up to 6 hours after symptom onset, but showing that the benefit was greatest in patients treated within 3 hours.<sup>71</sup>

#### *2.4.2.5 Age*

The randomized trials described above included a very limited number of patients aged >80 years. In effect, the ECASS trials specifically excluded this age group,<sup>38,39</sup> and the license for alteplase in the European Union therefore excluded this age group. The third International Stroke Trial (IST-3), published in Lancet 2012, included more than 3000 patients, of whom 53% were older than 80 years of age; the results supported that the benefits of IVT did not seem to be diminished in elderly patients.<sup>74</sup> In recent years the effectiveness and safety of thrombolysis in the elderly have been addressed in systematic reviews<sup>75</sup> and meta-analyses,<sup>76</sup> in registry based observational studies from SITS-ISTR<sup>77</sup> and VISTA (the Virtual International Stroke Trials Archive)<sup>78</sup> as well as in controlled comparison of SITS-VISTA.<sup>79</sup> The overall results indicate generally poorer outcome in this age group compared to younger patients, but with an association between thrombolysis and outcome similar to that for younger age groups.

#### 2.4.2.6 *Summary*

Thanks to intravenous thrombolysis, stroke care has developed over a 20 years period from being a “low-priority” disease to an acute emergency necessitating high priority and fast action. Since the time window for IVT was extended from the initial 3 hours up to 4.5, more patients were eligible for care. In Sweden the proportion of stroke patients that were given IVT had increased to 12% in 2014 (compared with 3% in 2005).<sup>4</sup> Still, many stroke patients do not benefit from treatment and the number of stroke patients needed to treat to obtain one positive outcome (NNT) remains high. The search for alternative or complementary methods has consequently continued parallel to the development of intravenous thrombolysis.

#### 2.4.3 **Intra-arterial thrombolysis**

Three randomized trials have found that intra-arterial infusion of recombinant prourokinase or urokinase within 6 hours of onset has some effect.<sup>56,80,81</sup> In all three trials the stroke had to be caused by an occlusion of the middle cerebral artery, M1- or M2-segment. In Prolyse in Acute Cerebral Thromboembolism (PROACT)<sup>80</sup> and PROACT II<sup>56</sup> both the intervention group and the control group were treated with heparin bolus and 4 hour infusion, and in the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT)<sup>81</sup> only with a bolus. In PROACT, the intervention group received intra-arterial infusion, of 6 mg recombinant prourokinase in the thrombus infused over two hours, and the control group received intra-arterial placebo. In PROACT II the dose was 9 mg infused over two hours, but no infusion was given to patients in the control group. In MELT various doses of urokinase were given intra-arterially to the intervention group. PROACT showed increased recanalization rate after intra-arterial treatment (IAT) compared to heparin alone, and PROACT II showed increased rate of favourable clinical outcome (mRS 0-2). MELT failed to show benefit in its primary endpoint (mRS 0-2), but showed increase in excellent outcome, mRS 0-1.

Since the control groups were not given intravenous thrombolysis it is not known whether IVT in this design would have had better outcome than IAT, as questioned in a meta-analysis by WJ Powers.<sup>82</sup> One of the problems regarding IAT is the long procedure time; an infusion of fibrinolytic agents took 2 hours in all of these studies.

#### 2.4.4 **Mechanical thrombectomy**

The idea of removing the thrombus mechanically emerged gradually and in small scale. There were attempts made with surgical operation, for example at the Mayo Clinic, presented in 1985.<sup>83</sup> Early endovascular attempts were made, one of them in Gothenburg in Sweden, where Dr. Gunnar Wikholm was one of the first to develop a technique to perform

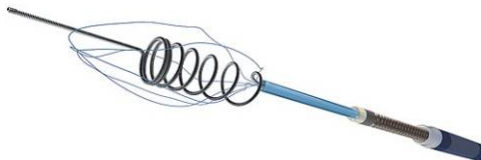
mechanical embolectomy in cerebral vessels. The first attempts were on cases in which a thromboembolic complication had occurred during an endovascular procedure of other cause, published already 1998,<sup>84</sup> and later performed on patients with primary acute ischemic stroke.<sup>85</sup> A snare (Amplatz GooseNeck) was introduced through a micro catheter to entrap the embolus. The results were good, and in Gothenburg this technique has been used with success.<sup>86</sup> Another early attempt was made by the use of a basket (Neuronet), presented by Mayer in 2002,<sup>87</sup> but there were also other variants such as the InTime and the EnSnare.<sup>88</sup>



**Figure 14.** The Amplatz GooseNeck Snare. (*Image reprinted with permission from Medtronic*)

#### 2.4.4.1 The Merci Retriever

The Merci Retrieval System was specifically designed and developed for percutaneous thromboembolectomy in brain vasculature.<sup>89</sup> It consists of a tapered wire with 5 helical loops of decreasing diameter (from 2.8 mm to 1.1 mm) at its distal end, to be advanced through the microcatheter in its straight configuration and resume its helical shape once delivered into the occluded intracranial artery, in order to ensnare the thrombus. In the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial they also used a Balloon Guide Catheter (BCG) with a balloon inflated in the internal carotid artery during thrombectomy in order to cause occlusion and through aspiration via the guide catheter reverse the blood flow and thereby reduce the risk of distal embolization.



**Figure 15.** The Merci Retriever.\* (*Image reprinted with permission from Stryker*)

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\* The Merci Retriever was also referred to as “the corkscrew”, due to its characteristic shape.

The safety and efficacy of the Merci Retriever to open occluded intracranial large arteries within 8 hours of the onset of stroke symptoms was reported in 2005.<sup>90</sup> All patients were ineligible for IVT. Recanalization was achieved in 46%, with significantly better outcome and lower mortality in the group with successful recanalization (mRS 0-2 in 46% versus 10%, mortality 32% versus 54%) compared to patients with unsuccessful recanalization. In 2006, Smith et al. reported further results from the MERCI study in the American Journal of Neuroradiology (AJNR). They had shown that mechanical thrombectomy after IVT was as safe as mechanical thrombectomy alone.<sup>91</sup>

#### 2.4.4.2 Aspiration

An alternative mechanical approach was introduced by The Penumbra System, which combined aspiration and extraction.<sup>92</sup> Aspiration was performed with a reperfusion catheter and an aspiration pump, which created a vacuum. On the same time a separator was advanced into the proximal thrombus. As an option thrombus could be extracted with a thrombus removal ring. Results presented 2009 by The Penumbra Pivotal Stroke Trial Investigators showed revascularization (TIMI 2 to 3) in 82%, mRS 0-2 in 25%, and a mortality of 33%.<sup>93</sup> Later results using the Separator 3D were more promising with mRS 0-2 in 43% at 90 days.<sup>94</sup>



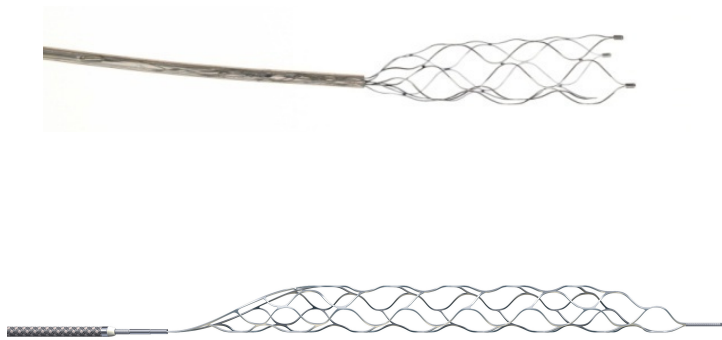
**Figure 16.** The Penumbra separators and aspiration pump. (*Image reprinted with permission from Penumbra Inc*)

#### 2.4.4.3 Stent-retrievers

A different kind of thrombectomy device was also developed in the form of a microcatheter-delivered highly flexible, fully retrievable intracranial stent.<sup>95</sup> When it was developed, the purpose was for endovascular treatment of intracranial aneurysms. The difference from most other intracranial stents was its ability to be retrieved and repositioned after complete



delivery. In 2008 and 2009, there were anecdotal reports of using the stent for thrombectomy, with good results.<sup>96,97</sup> Early results for the use of the Solitaire stent as a thrombectomy device were described in 2009 and 2010.<sup>97,98</sup> Later, there were several case series and studies conducted, all of which with promising results.<sup>99-106</sup> The Solitaire was later followed by several other variants of stent-retrievers, for example the Trevo device.<sup>107-110</sup>



**Figure 17.** The Solitaire device (above) and the Trevo device (below). (*Image reprinted with permission from Medtronic (Solitaire) and Stryker (Trevo)*)

In 2012, Davalos et al. published a retrospective study of 141 consecutive patients in six experienced European centres presenting with acute ischemic stroke treated with Solitaire FR as the first-line device to restore blood flow.<sup>111</sup> Revascularization was achieved in 85%, and mRS 0-2 in 55%, with lower mortality (20%) and less symptomatic hemorrhage (4%) than in the MERCI study (7.8%).

That same year (2012) results were also published from two randomized trials comparing the Merci Retriever with two different stent retrievers, Solitaire and Trevo.<sup>112,113</sup> Saver et al. performed the SWIFT (Solitaire With the Intention For Thrombectomy) trial with the primary endpoint TIMI 2 or 3 flow in all treatable vessels without symptomatic intracranial hemorrhage, which was achieved more often in the Solitaire group than in the Merci group (61% vs 24%).<sup>112</sup> More patients had good 3-months neurological outcome with Solitaire than with Merci (58% vs. 33%) and 90-day mortality was lower (17% vs. 38%). Nogueira et al. reported the results from Thrombectomy REvascularization of large Vessel Occlusions in acute ischemic stroke (TREVO) II in the same issue of Lancet.<sup>113</sup> The primary efficacy endpoint, TICI scores of 2 or 3 with the assigned device alone, was met in 86% of the patients in the Trevo group and in 60% of the patients in the Merci group. The incidence of the different procedure-related complications (primary safety endpoint) did not differ

significantly between the groups, 13 (15%) patients in the Trevo group vs. 21 (23%) in the Merci group.

#### *2.4.4.4 Randomized trials, 2013*

In March 2013, three randomized trials were published in the New England Journal of Medicine.<sup>114-116</sup> All of them failed to show superiority of endovascular treatment compared to standard treatment (including IVT). In the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) the aim was to evaluate mechanical thrombectomy, with either Merci Retriever or Penumbra System in two different groups of patients, with or without favourable penumbral pattern (determined by imaging), compared to standard treatment.<sup>114</sup> Patients were to be included within 8 hours after onset of large vessel, anterior circulation stroke. In the Interventional Management of Stroke (IMS) III study patients who had received IVT within 3 hours after symptom onset were randomly assigned to receive additional endovascular therapy or IVT alone.<sup>115</sup> In the Local versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS) study, patients were randomly assigned to either endovascular therapy (IAT, mechanical clot disruption or retrieval) or IVT, within 4.5 hours after onset.<sup>116</sup>

These three trials have all been questioned, for a number of different reasons.<sup>117-123</sup> In MR RESCUE 22 participating centres enrolled 118 patients during the period from 2004 through 2011. On average, each participating centre enrolled 1 patient every 16 months, which may suggest that inclusion in the trial was selective and not representative of patients with stroke in general. The rate of good outcome was also substantially lower for both treatment methods (19% in MR RESCUE compared to 42 and 44% in IMS III and SYNTHESIS respectively), which makes evaluation of a diagnostic tool (imaging-based penumbral pattern) questionable.<sup>120</sup> The number of patients per centre per year was small also in the other two trials. In both IMS III and SYNTHESIS, patients were randomized partly without radiological proof of an occluded vessel, and there was no evaluation of the salvageable brain with perfusion CT or MR. In all these 3 trials mainly older devices, Merci or Penumbra, were used, and many patients only received intra-arterial thrombolysis instead of thrombectomy.

The impact of these three trials published in the same issue of NEJM was substantial. In the United States, insurance companies were considering withdrawal of reimbursement for thrombectomy devices for all ischemic stroke patients.<sup>124</sup> The studies also sparked an intense research effort, where efforts were made to avoid the design flaws in the trials mentioned above.

#### 2.4.4.5 *Randomized trials, 2015*

In early 2015, five new randomized trials were reported.<sup>125-129</sup> The first one to be published was the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), published in January 2015, with preliminary results presented in October 2014.<sup>125</sup> Eligible patients had a confirmed proximal occlusion in the anterior circulation and could be treated intra-arterially within 6 hours after symptom onset. The study included 500 patients, and convincingly demonstrated superiority for mechanical thrombectomy by stent retriever together with standard treatment (89% IVT) compared with standard treatment (90% IVT alone). The primary outcome was mRS 0-2 at 90 days, where the results were 32.6% vs. 19.1%, in favour of endovascular treatment. There were no statistically significant differences in mortality or in the occurrence of symptomatic intracerebral hemorrhage between the two groups.

After the announcement of the results from MR CLEAN several other randomized trials were halted and interim analyses were performed. Since the results were in significant favour for mechanical thrombectomy, four trials were stopped early and the results published.

The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial included patients with a proximal intracranial occlusion in the anterior circulation up to 12 hours after symptom onset.<sup>126</sup> They compared standard care (control group) to standard care plus endovascular treatment at 22 centres worldwide, and included 316 patients. Eligible patients had an occluded proximal cerebral artery in the anterior circulation, ASPECTS 6-10 and moderate to good collateral circulation, defined as filling of 50% or more of the pial arterial MCA circulation on CT angiography (preferably multiphase). The rate of functional independence was increased in the intervention group (53.0%) compared to the control group (29.3%), and the intervention was associated with reduced mortality (10.4%) vs. the control group (19.0%).

The Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT-PRIME) trial was performed at 39 centres in the United States and Europe, and included 196 patients.<sup>127</sup> Patients with confirmed occlusions in the proximal anterior intracranial circulation and an absence of large ischemic-core lesions, who were receiving or had received intravenous tPA, were assigned to tPA alone (control group) or to undergo additional endovascular thrombectomy with the use of a stent retriever within 6 hours after symptom onset. Modified Rankin scale score 0 to 2 at 90 days was higher in the intervention group than in the control group (60% vs. 35%). There were no statistically significant between-group differences in 90-day mortality (9% vs. 12%) or symptomatic intracranial hemorrhage (0% vs. 3%).

The Extending the Time for Thrombolysis in Emergency Neurological Deficits – Intra-Arterial (EXTEND-IA) trial, performed in Australia and New Zealand, tested whether more

advanced imaging selection, recently developed devices and earlier intervention would improve outcome.<sup>128</sup> All 70 patients received IVT within 4,5 hours after symptom onset and were randomized to either IVT alone or combined with endovascular treatment. All the patients had occlusion of the internal carotid or middle cerebral artery, evidence of salvageable brain tissue and ischemic core of less than 70 ml on CT perfusion imaging. The trial was stopped early because of efficacy after 70 patients had undergone randomization (35 patients in each group). Functional independence at 90 days was 71% in the intervention group and 40% in the group receiving IVT alone, without any significant differences in rates of death or symptomatic intra cerebral hemorrhage.

The Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset (REVASCAT) was a study conducted at four centres in Catalonia, Spain, and included 206 patients.<sup>129</sup> Treatment had to start within 8 hours and mechanical thrombectomy was considered if IVT was ineffective or contraindicated. The control group consisted of medical treatment alone (IVT if eligible). Modified Rankin Scale score 0-2 at 90 days was 43.7% vs. 28.2%, in favour of intervention.

After the publication of these five trials with positive results for mechanical thrombectomy several meta-analyses have been performed, confirming the results.<sup>130-135</sup> The meta-analyses showed clear evidence for improvement in functional independence with endovascular thrombectomy compared with standard medical care.

#### *2.4.4.6 Consequences*

After the initial three randomised trials were presented with non-favourable results for mechanical thrombectomy, five more randomized trials have refuted these initial results. This led to a rapid change of treatment recommendations for mechanical thrombectomy after acute stroke, supported by the European Stroke Organisation (ESO), European Society of Minimally Invasive Neurological Therapy (ESMINT), European Society of Neuroradiology (ESNR), and European Academy of Neurology (EAN).<sup>136</sup> The changes were that mechanical thrombectomy, in addition to IVT when eligible, is now recommended treatment for acute stroke patients with a large artery occlusion in the anterior circulation within 6 hours from stroke onset. Thrombectomy should be performed as soon as possible. If IVT is contraindicated, mechanical thrombectomy should be performed as first-line treatment. Patients with basilar artery occlusion could also be treated with thrombectomy, or treated within a randomized trial (approved by local ethical committee). The American Heart Association/American Stroke Association (AHA/ASA) has also published new treatment recommendations, in which thrombectomy is recommended in large artery occlusions (internal carotid artery (ICA) or proximal MCA) within 6 h of symptom onset and with NIHSS score of 6 or more, ASPECTS of 6 or more and prestroke mRS score 0 to 1.<sup>137</sup>

#### 2.4.4.7 *Randomized trials, 2016*

Recently, in the end of august 2016, the results from The THRoMbectomy des Artères CErebrales (THRACE) trial was published.<sup>138</sup> This trial was designed in 2009 before the results of the IMS III trial became available and had a similar protocol, comparing IVT plus thrombectomy to IVT alone. The patients were not selected on image-based criteria, except that a large vessel occlusion had to be present. In France, 26 centres included a total of 414 patients between June 1, 2010 and Feb 22, 2015. The study was halted early (planned for 480 patients) after an interim analysis showing superiority for the intervention group. Functional independence, mRS 0-2, was 53% in the intervention group compared to 42% in the IVT alone group, with an OR 1.55, 95% CI 1.05 – 2.30. There were 59 patients (29%) in the intervention group that did not have thrombectomy. Time from randomization (performed after IVT, and therefore only affecting the group randomized to receive additional thrombectomy) to groin puncture was considerably higher than in other trials, which may partly explain the reduced difference between the groups compared to the studies published in 2015.

Even more recently, in September 2016, the results from The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke (THERAPY) was published in Stroke.<sup>139</sup> The study was designed to evaluate the potential benefit of IVT plus aspiration thrombectomy with the Penumbra System (instead of using for example a stent retriever) compared to IVT alone. The study was halted early, after inclusion of 108 of 692 planned patients, based on the favourable results from the five randomized trials mentioned above. THERAPY did not meet its primary end point, mRS 0-2, but it did demonstrate a direction of effect toward benefit.

### 2.4.5 **Special considerations concerning the posterior circulation**

All the randomized trials on thrombectomy that have been described above concern the anterior circulation. Anterior circulation stroke is more common, with posterior circulation stroke accounting for only about 20% of all ischemic strokes.<sup>140</sup> The NIHSS and ASPECTS are both designed for anterior circulation stroke, and symptoms from the posterior circulation are often more diffuse, including decreased level of consciousness, visual disturbances, vertigo and nausea, apart from more obvious symptoms of stroke such as hemiparesis and speech impairment. Acute severe brainstem stroke with angiographically proven vertebrobasilar artery occlusion has a poor prognosis if untreated, with a mortality rate of at least 75%.<sup>141</sup>

In 2009, the Basilar Artery International Cooperation Study (BASICS) was published in the Lancet.<sup>140</sup> It was a prospective registry study concerning treatment and outcomes of acute basilar artery occlusion. Both IVT and IAT were analysed, with very poor outcome in both groups. Intra-arterial treatment in this study was in the majority of cases treatment by intra-

arterial thrombolysis alone, but in some cases IAT was combined with mechanical thrombectomy and in a minority of cases the treatment was thrombectomy alone. Their results did not support unequivocal superiority of IAT over IVT.

There have been several case series addressing intra-arterial thrombolysis as therapy of basilar artery occlusion, many of the larger ones discussed in a systematic analysis by Lindsberg et al. 2006, in which the authors concluded that the effect of IVT probably does not differ much from the effect of IAT.<sup>142</sup> In their analysis of 420 patients (from 3 studies of IVT and 10 studies of IAT), 24% of patients treated with IAT and 22% of patients treated with IVT reached good outcomes. They also compared patients in whom recanalization had occurred to patients without recanalization, in which 38% versus 2% reached good outcome. There were 40/76 (53%) deaths in the IVT patients and 190/344 (55%) after IAT.

Treatment of basilar occlusion with mechanical thrombectomy has shown good results in several case series<sup>143-148</sup>. In 2015, Gory et al. performed a systematic review of basilar artery occlusions treated with stent retrievers.<sup>149</sup> The review included sixteen studies, altogether showing a good outcome (mRS 0-2) in 42%, with a recanalization rate of 81%, and a mortality of 30%.

### **3 AIMS**

The overall aim of this doctoral thesis was to study the outcome and safety of mechanical thrombectomy. By analysing the outcome for patients treated at the Karolinska University hospital, we aimed to contribute to the knowledge about outcome and safety for this technique (Study I, II and III).

When this doctoral project started, the technique of mechanical thrombectomy was still developing and published results were promising, but no large randomized trial had been performed. An initial aim was to use data from the Swedish national stroke registry and compare patients who were treated medically to patients who underwent mechanical thrombectomy at our hospital. In this way we hoped to be able to assess the value of the technique without having to perform a randomized study, since we had ethical considerations about randomizing patients due to the good local results with mechanical thrombectomy.

Due to the rapid knowledge development of the field, and especially after the positive results from several randomized trials published 2015, we had to partly review our aims:

Firstly, we performed a meta-analysis of the randomized trials (Study IV).

Secondly, since the positive results from the randomized trials led to new treatment recommendations, which in many way were similar to what had been in practice at our hospital during the study period, we used data from the Riksstroke database and from the local treatment database in Stockholm to assess the potential demand for mechanical thrombectomy if all residents in Sweden were offered treatment according to the new recommendations (Study V).

## **4 MATERIAL AND METHODS**

### **4.1 SETTING**

The Department of Neuroradiology at Karolinska University Hospital is the sole provider of neuroendovascular treatments in a catchment area of approximately 2 million, and during the study period, acute endovascular stroke treatment was provided by initially three and eventually four\* designated neurointerventionists on a 24/7 basis.

Study I comprised all patients treated with thrombectomy for acute basilar artery thrombosis at the department of neuroradiology, Karolinska University Hospital, Stockholm, from September 2005 to November 2010. During the study period, mechanical thrombectomy was the preferred treatment for basilar artery occlusion and there were no patients with basilar artery occlusion treated with intravenous thrombolysis only.

In study II, every patient treated with mechanical thrombectomy for acute ischemic stroke from September 2005 through December 2011 was included. From the same material we then extracted patients with anterior circulation stroke, and these patients were analysed in more detail in Study III. The patients with anterior circulation stroke during the years 2009-2011 were also used as a comparison to patients from the Swedish National Stroke Registry, Riksstroke, in study V.

Study IV was a meta-analysis of six randomized multicentre trials from different parts of the world.

### **4.2 STUDY I-III AND THROMBECTOMY PATIENTS IN STUDY V**

#### **4.2.1 Patient selection**

Patients were either admitted directly to the Karolinska University Hospital or transferred from one of six referring hospitals within the region. In addition, patients were occasionally sent from more distant hospitals outside the primary catchment area.

The selection of patients for thrombectomy was based on both clinical and radiological parameters. The decision to perform thrombectomy, or not, was taken jointly by the neurointerventionist and the stroke neurologist on call, and was dependent on many factors, such as areas of already manifest infarction, location of thrombus, tortuosity of vessels, extra cranial stenosis or dissection, co-morbidities, time, age and clinical judgement.

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\* The author of this thesis.



#### *4.2.1.1 Clinical selection*

In the anterior circulation, patients with NIHSS scores of 8-30 (scores changed to 6-25 in 2010) without severe comorbidities were eligible for thrombectomy. Exceptions were made for some patients with an NIHSS score less than 6 when symptoms included aphasia. If there were no contraindications, all eligible patients were treated with intravenous thrombolysis (IVT).

There was no clear definition of severe comorbidity, rather was it up to the neurologist on call together with the neurointerventionist to decide. Generally severe heart failure, advanced dementia, terminal cancer and other major diseases were regarded as a contraindication to thrombectomy. Many diseases adding up together could also be considered as a contraindication.

Age was not considered to be a limit, but in patients above 80 years of age special care was taken to evaluate the potential for rehabilitation.

Time from onset of stroke symptoms was not a definite criterion; we tried to rely more on radiological appearance than on time from stroke onset. As a rule of thumb we were reluctant to treat patients with anterior circulation stroke later than 8 hours, and patients with posterior circulation stroke later than 16 hours after onset. Of course, we preferred to treat patients as quickly as possible, and took great care in minimizing the time from arrival to hospital to groin puncture – an especially difficult task if patients needed to be transferred between hospitals.

In posterior circulation stroke it can be very difficult to predict which patients would benefit from thrombectomy, since even unconscious patients may recover well. We regarded fluctuating symptoms as a good sign. When study I was performed, the NIHSS score was not systematically registered for this patient category, but GCS was. Patients in study I did not receive IVT.

#### *4.2.1.2 Radiologic selection*

Patients were evaluated with non-enhanced CT, which was complemented with CT perfusion (CTP) and CT angiography as soon as a hemorrhage had been excluded. Based on imaging, mechanical thrombectomy was considered for all patients with remaining symptoms, large-vessel occlusion and with salvageable brain tissue as interpreted from the CT, CTP, and CT angiography. The role of CTP in the workup was to assess if there were areas of tissue with normal or next to normal blood volume in areas with restricted perfusion, i.e. that there would be viable tissue (penumbra) to save with revascularization. There were no formal limits on CTP that hindered treatment; rather CTP was regarded as one piece of a puzzle together with the other factors describe here. In case of severe renal failure, CTP was not performed.

MRI was mostly used in cases of unconscious patients with posterior circulation stroke, in which we wanted to evaluate the extent of manifest infarction in the brainstem and cerebellum.

#### **4.2.2 Procedure**

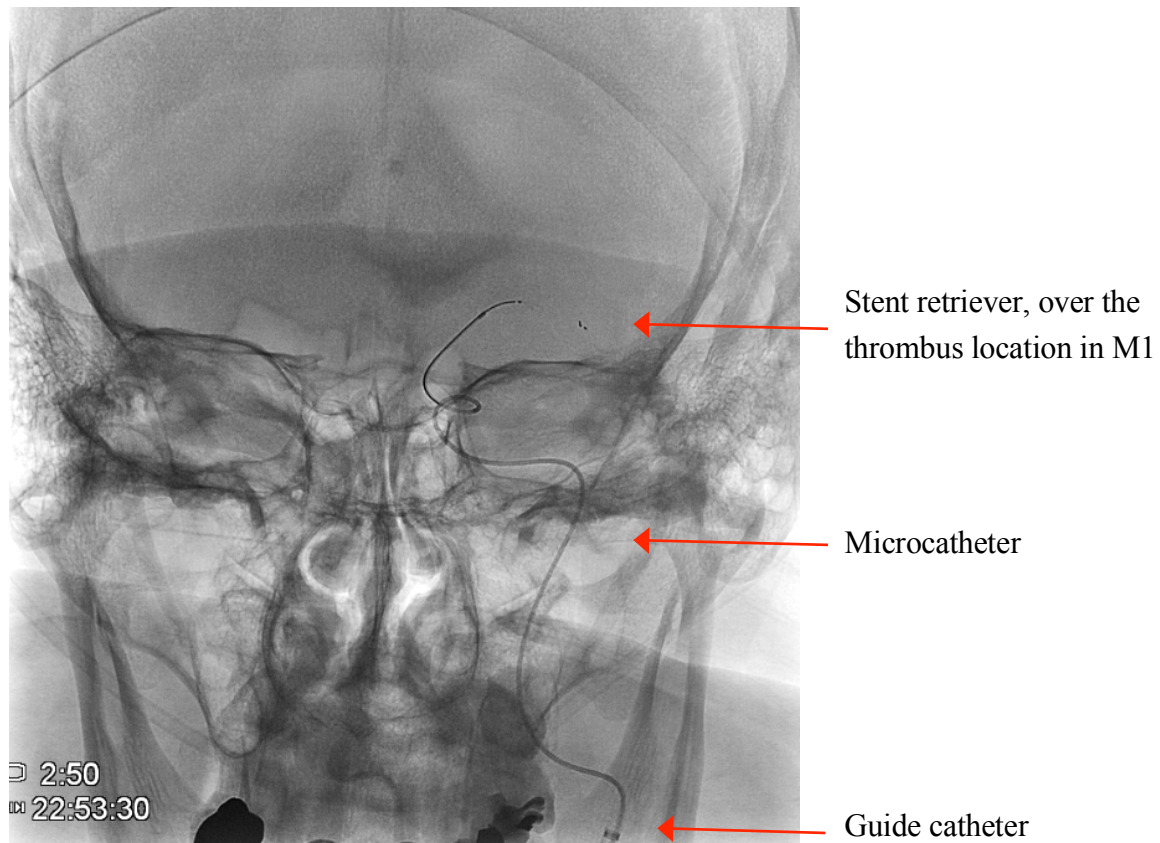
Study I (basilar occlusion) included patients from 2005-2010, during the first years of which different variants of the Merci Retriever were used. In the spring of 2009 we started to use stent-retrievers and from summer 2009 we almost exclusively used stent-retrievers. The device was usually delivered through a 6 French (F)<sup>\*</sup> Envoy catheter, but depending on the size of the vertebral artery and of the choice of the operator, sometime a 7 or 8 F guide catheter was used instead. Study II and III includes patients from 2005-2011 and study V includes patients only from the years 2009-2011 and therefore a relatively higher number of stent-retrievers was used. In the anterior circulation strokes, most often a long 8 F Arrow introducer sheath was placed in the common carotid artery, followed by an 8 F Merci balloon guide catheter in the internal carotid artery. After confirming the presence of the thromboembolus on an angiogram, a microcatheter was advanced through the thrombus with the aid of a microguidewire. After release of the stent retriever, centred at the obstructive blood clot, it was left in place for approximately 5 min (3–10) before the actual thrombectomy was performed. The balloon was inflated with simultaneous aspiration in the guide catheter to create flow reversal in the internal carotid artery (ICA) during the thrombectomy. For early cases in the series, where the Merci device was used, the device was positioned distal to the thromboembolus. In the vertebral arteries no balloon guide catheter was used.

For patients with so-called tandem occlusions in the anterior circulation, an occlusion in the proximal ICA due to acute dissection or atherosclerosis in addition to a distal ICA or middle cerebral artery (MCA) occlusion, the procedure was modified to include angioplasty or carotid stenting. Placement of a stent, either extra- or intracranial, was, however, avoided when possible due to the need for anti-platelet aggregation therapy, which in the context of a potential acute ischemic infarct was considered to impose a risk for a severe reperfusion hemorrhage.

As a supplement to thrombectomy for treating small distal emboli, alteplase was sometimes infused intra-arterially in combination with careful microcatheter and microguidewire manipulations.

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<sup>\*</sup> 1 French is exactly 1/3 millimeter.



**Figure 18.** Frontal view, showing the tip of the guide catheter placed in the left internal carotid artery from which the microcatheter extends to the stent retriever, which is in position over the thrombus (not seen) in the middle cerebral artery.

### 4.3 BASELINE AND OUTCOME PARAMETERS

For study I-III and partly V, baseline and outcome data were retrieved from computerized records at the hospital. ASPECTS and mTICI scores were assessed. Time from onset of stroke symptoms to groin puncture was noted. Patients who went to sleep with normal status and woke-up with stroke symptoms were classified as “wake-up” strokes. This group could also include some patients found with stroke symptoms and unknown time of onset (no known “last seen well”-time). In study IV (the meta-analysis) data were received from the already published randomized trials. Data of stroke patients from all of Sweden for study V was given from Riksstroke, the Swedish National Stroke Register.

#### 4.3.1 Pre intervention

GCS (study I only), NIHSS score and ASPECTS were used to assess stroke severity. GCS and NIHSS scores were considered in the acute setting, whereas no scoring scale was used to

evaluate the unenhanced CT acutely; the scoring according to ASPECTS was performed retrospectively. Sex and age were noted. Different aspects of time were studied in the different studies (I-III); time from onset to arrival to the Karolinska University Hospital, time from onset to groin puncture or from groin puncture to first revascularization.

#### **4.3.2 Post intervention**

The use of stent retriever or older devices was noted in study II. Revascularization was assessed using mTICI. A post-procedure mTICI score of 2b or 3 was considered to represent a successful revascularization. Severe adverse events were noted, most interesting being the presence of symptomatic hemorrhage (according to SITS-MOST-definition).<sup>54</sup> NIHSS score was of course also of great importance after the procedure, and was compared to the pre-interventional score. ASPECTS was also noted on follow-up CT, and compared to the pre-interventional score.

#### **4.3.3 Long-term follow-up**

The primary outcome measurement in all of the studies was modified Rankin Scale (mRS) score at 3 months, with functional independence (mRS 0-2) regarded as a good outcome. Mortality equals mRS 6.

### **4.4 META-ANALYSIS (STUDY IV)**

Only complete, randomized controlled trials published in their entirety were considered for inclusion. The intervention group was endovascular treatment in addition to IVT, the control group was IVT, and at least two-thirds of all participants had to have received IVT. PubMed, the Cochrane Central Register of Controlled Trials, and the National Institutes of Health Clinical Trials were searched from the date of inception until 17 April 2015.

The primary specified outcome was the proportion of patients with mRS score 0–2 at 90 days from stroke onset. Secondary outcomes included mRS score 0–1 at 90 days, mRS score 0–3 at 90 days, mortality at 90 days, intracerebral hemorrhage within 90 days, and mRS score 5–6 at 90 days. To maintain high homogeneity between the included trials, the subgroup of patients from the IMS-III trial that did not have vessel occlusion on imaging were excluded from further analysis.

## **4.5 RIKSSTROKE (STUDY V)**

The National Stroke Registry in Sweden, Riksstroke, intends to register all patients with acute stroke treated in Sweden, the coverage calculated to be 85-95% during the study period (2009-2011). The number of thrombectomies began to be registered in 2009. From Riksstroke we collected information on patients from all of Sweden for the time period corresponding to our database. Patients with an anterior circulation stroke, who arrived primarily (without any pre-hospital triage) to Karolinska University Hospital, Solna, 2009-2011 and were treated by thrombectomy, were analyzed and compared to the total number of patients treated for ischemic stroke at Karolinska. We assumed that the proportion of performed thrombectomies among the unselected patients arriving primarily to our hospital, divided in specified intervals on the NIHSS (0-5, 6-11, 12-19 and 20-25), would represent the proportion of patients potentially eligible for thrombectomy if other hospitals followed the same practice. By using data from the most recent available annual report from Riksstroke, we estimated the number of stroke cases in each defined NIHSS category and compared it to the proportion of performed thrombectomies at Karolinska, in order to estimate the potential number of thrombectomies in Sweden if all hospitals selected patients according to the new guidelines published in 2015 and 2016.<sup>136,137</sup>

## **4.6 STATISTICS**

### **4.6.1 Study I-III and V**

For the statistical analysis, we used SAS statistical software (V.9.1; SAS Institute Inc.). Ninety-five percent confidence intervals (95 % CI) were calculated assuming a binomial distribution. For testing independence between outcome and exposure variables, we used Pearson's exact chi-squared tests. Observations with missing values were excluded. A p-value of <0.05 was considered statistically significant.

Since a delayed assessment of mRS score may lead to an overestimation of patients with good outcome, we assessed the potential impact of the delayed mRS assessments by doing sensitivity analyses where an extra point was added to the mRS score for all patients who were assessed after more than 6 months (study I and II).

Tests for trends and multivariate regression analyses were done by analysing categories as continuous variables in logistic regression using the PROC LOGISTIC statement in SAS (study III).

The studies were approved by the research ethics committee at Karolinska Institutet.

### **4.6.2 Study IV (meta-analysis)**

Two independent reviewers performed the statistical analyses using Review Manager

(RevMan, V.5.3., Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Review Manager was used for data presentation. Data were pooled in the intervention group and the control group. Outcome heterogeneity was evaluated with Cochrane's Q test (significance level cut-off value at  $<0.10$ ) and  $I^2$  (significance cut-off value  $>50\%$ ). A p-value of  $<0.05$  was considered statistically significant. The Mantel–Haenszel method was used for dichotomous outcomes with fixed effect or random effect (DerSimonian and Laird)<sup>150</sup> where appropriate, according to outcome heterogeneity. Odds Ratio (OR) with 95% CI were calculated for all outcomes.

## 5 RESULTS

### 5.1 STUDY I-III

#### 5.1.1 Baseline data

In study I, we included 28 patients with acute basilar artery occlusion, 8 women and 20 men. At admission, 14 of 28 had GCS of 8 or less. The number of pre-procedure acute infarcts was 4 out of 8 (50%) women and 2 out of 20 (10%) men ( $p=0.038$ ). Treatment was initiated within 6 hours from stroke onset in 19 patients.

In study II, we included 240 patients, and of these 192 (80%) had an anterior circulation stroke. There were 138 (57.5%) men and 102 (42.5%) women. Of all patients, there were 45% under the age of 65, 46% between 65 and 79 years of age, and 9% were 80 years or older. The median NIHSS score, all patients included, was 16. In patients with anterior circulation stroke the figure was the same, but for patients with posterior circulation stroke the median NIHSS score was 11. IVT before the endovascular intervention was administered to 96 patients (40%). Baseline mRS, reflecting the functional status of the patient before stroke onset, was 1 or more in 18%.

Among the 192 patients with anterior circulation stroke (the material also used in study III and patients from 2009-2011 in study V) there were 104 (54%) men and 88 (46%) women, with a mean age of 64.1 years and a median age of 66 years. The distribution by age was basically the same as for the complete material. The median ASPECTS was 8. Pre-intervention IVT was given to 89 patients (46%), and of these patients 44% were women. In 84% of the cases the functional status before the current stroke was excellent (baseline mRS score 0), and in 16% the mRS score was 1 or more. In 71% of the cases, stent retrievers were used, and in 15%, a non-stent retriever was utilized (mostly the Merci Retriever, in a few cases the Amplatz GooseNeck Microsnare). In 4% of the cases, a combination of stent retriever and non-stent retriever was used. In 7% of the cases, no retriever at all was used, but instead mechanical manipulation and intra-arterial thrombolysis were performed.

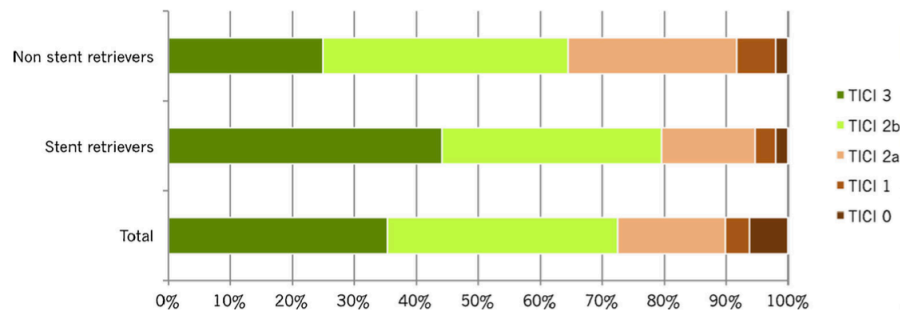
			Anterior and posterior circulation		Anterior circulation					
					All		IV tPA		No IV tPA	
			nr	%	nr	%	nr	%	nr	%
All			240	100.0	192	100.0	89	100.0	103	100.0
Sex	Male		138	57.5	104	54.2	50	56.2	54	52.4
	Female		102	42.5	88	45.8	39	43.8	49	47.6
Age	16–49		38	15.8	29	15.1	15	16.9	14	13.6
	50–64		70	29.2	56	29.2	22	24.7	34	33.0
	65–79		110	45.8	89	46.4	46	51.7	43	41.7
	80–xx		22	9.2	18	9.4	6	6.7	12	11.7
mRS baseline	0		202	84.2	161	83.9	79	88.8	82	79.6
	1		26	10.8	21	10.9	7	7.9	14	13.6
	2		9	3.8	7	3.6	3	3.4	4	3.9
	3		2	0.8	2	1.0	0	0.0	2	1.9
	4		1	0.4	1	0.5	0	0.0	1	1.0
Time to Karolinska	Within 3 h		95	39.6	80	41.7	38	42.7	42	40.8
	3–4.5 h		45	18.8	34	17.7	27	30.3	7	6.8
	More than 4.5 h		33	13.8	25	13.0	14	15.7	11	10.7
	In hospital		32	13.3	26	13.5	4	4.5	22	21.4
	Wake up		28	11.7	22	11.5	4	4.5	18	17.5
	Missing		7	2.9	5	2.6	2	2.2	3	2.9
iv rtPa			96	40.0	89	46.4	89	100.0	0	0.0
NIHSS pre-thrombectomy (median =16)	0–5				6	3.1	1	1.1	5	4.9
	6–11				39	20.3	17	19.1	22	21.4
	12–19				91	47.4	48	53.9	43	41.7
	20–35				52	27.1	22	24.7	30	29.1
	Missing				4	2.1	1	1.1	3	2.9
pre-ASPECT	0–5				29	15.1	18	20.2	11	10.7
	6–7				57	29.7	29	32.6	28	27.2
	8–9				72	37.5	35	39.3	37	35.9
	10				32	16.7	7	7.9	25	24.3
	Missing				2	1.0	0	0.0	2	1.9
Time to groin puncture	Within 3 h	27	11.3		23	12.0	9	10.1	14	13.6
	3–4.5 h	59	24.6		50	26.0	25	28.1	25	24.3
	More than 4.5 h	87	36.3		66	34.4	45	50.6	21	20.4
	In hospital	32	13.3		26	13.5	4	4.5	22	21.4
	Wake up	28	11.7		22	11.5	4	4.5	18	17.5
	Missing	7	2.9		5	2.6	2	2.2	3	2.9
mTICI pre-thrombectomy	0	219	91.3		180	93.8	83	93.3	97	94.2
	1	10	4.2		6	3.1	4	4.5	2	1.9
	2a	6	2.5		3	1.6	0	0.0	3	2.9
	2b	2	0.8		1	0.5	1	1.1	0	0.0
	Missing	3	1.3		2	1.0	1	1.1	1	1.0

**Table 1.** Study II: Patient characteristics by thrombus location and pre-intervention IVT.<sup>151</sup>  
The patients with anterior circulation stroke were also included in study III.

### 5.1.2 Angiographic results

In study I (basilar artery) 64% of patients had a successful recanalization (mTICI score 2b or 3), and in study II (both anterior and posterior circulation, including the patients studied in study I) 72% had a successful recanalization. If only stent retrievers were used (study II) the rate of mTICI score 2b and 3 were 80%, to compare with 66% if only non-stent retrievers were used (mostly the Merci Retriever). Even when only anterior circulation stroke was accounted the rate of successful recanalization was 72%.



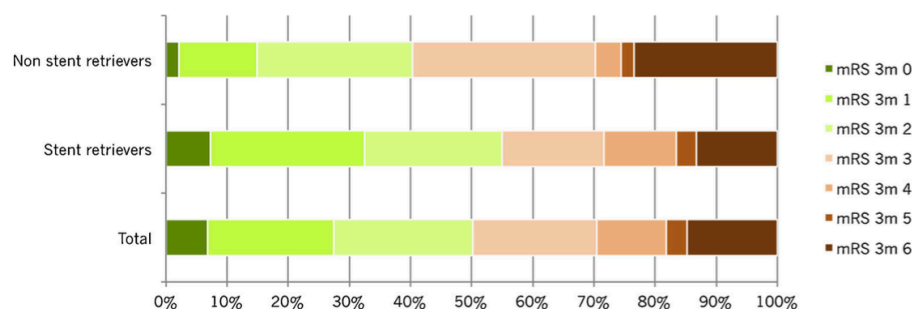


**Figure 19.** Study II: mTICI score post-thrombectomy, total (237 patients), stent retrievers (151 patients), and non-stent retrievers (mainly Merci) (47 patients).

### 5.1.3 Clinical results

In study I, the overall proportion of patients with a favourable outcome (mRS 0-2) was 57% (95% CI 37%-75%). There were six deaths (21%, 95% CI 8% to 41%) in the cohort. There was a strong negative association between outcome and CT detectable pre-procedure infarction ( $p=0.002$ ). Among patients without signs of acute infarction on non-enhanced CT scan prior to treatment, the proportion with a favourable outcome was 73% (95% CI 50% to 89%). The proportion of deaths in this cohort was 9% (95% CI 1% to 29%). None of the patients with signs of acute infarction prior to treatment had a favourable outcome.

In study II, 50% (120/240) of all patients reached a good functional outcome (mRS 0–2). In the subgroup of patients with an anterior circulation stroke the proportion was almost identical (49%, 95/192). Patients that had received IVT before the intervention had a good functional outcome in 47% (42/89), compared to 51% (53/103) of patients that did not receive IVT. For patients with no functional deficit prior to stroke onset (mRS score 0 prior to stroke onset), the proportion with good functional outcome was 54%. In patients with an anterior circulation stroke the median NIHSS score was 16 prior to thrombectomy and 7 afterwards, thus a reduction of 9 points. The median ASPECTS was 8 prior to treatment and 7 afterwards. At three months, 13.5% of patients with stroke in the anterior circulation were deceased (mRS 6), for both anterior and posterior circulation stroke cases the same figure was 14.5%. When stent retrievers were used recanalization and a good functional outcome was achieved more often than with non-stent retrievers, although not statistically significant (figure 19 and 20).



**Figure 20.** Study II: mRS score 3 months post-thrombectomy, total (237 patients), stent retrievers (151 patients), and non-stent retrievers (mainly Merci) (47 patients).

In study III, we found a statistically significant association between age and good functional outcome in unadjusted analysis. Patients younger than 50 years of age achieved a mRS score of 0-2 in 79%, compared to 39% of the patients older than 80 years of age. For patients without prior functional deficits (mRS score 0 before stroke onset), the difference was less (81% compared to 54%) but still significant. Patients aged 50-64 achieved mRS 0-2 in 47% and those aged 65-79 in 44% (50% and 49% respectively, if mRS 0 before stroke). As expected, there was an association between pre-thrombectomy NIHSS score and mRS score at 3 months ( $P = 0.0001$ ). We also found an association between pre-thrombectomy ASPECTS and mRS score, although the latter was not statistically significant ( $P = 0.064$ ). There was no statistical association found between time from symptom onset to groin puncture and functional outcome, but this analysis also included patients with wake-up stroke. A statistically significant association was found between grade of recanalization (mTICI post) and improvement in NIHSS score as well as with functional outcome. There was no suggestion of poorer outcome for patients older than 80 years of age, compared to those aged 50-64 or 65-79, when both pre-treatment infarct size, pre-treatment NIHSS score, time to treatment, and age were included in a multivariate regression analysis, but in the oldest age category only 1 patient was included with ASPECTS 6-7 and no patient with ASPECTS 0-5 (table 2). We found that in elderly patients we had had a tendency to select patient with higher ASPECTS than in younger patients. Interestingly, patients younger than 50 years of age did significantly better, even though 69% of patients in this age group had an ASPECTS  $\leq 7$ .

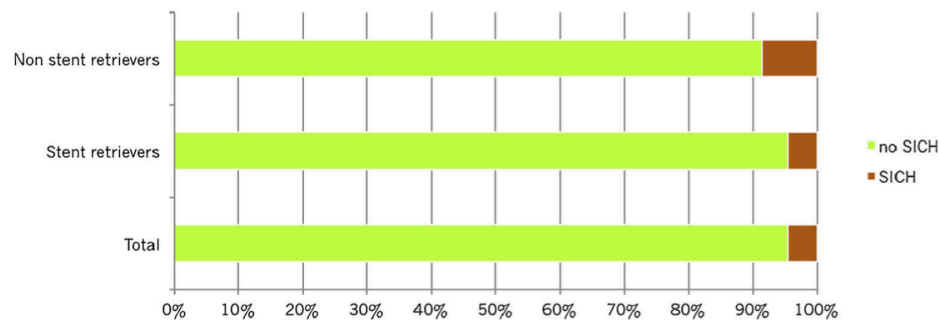
There were 22 patients with wake-up stroke in study III, of which 14 (63.6%) patients had a reduction in the NIHSS score of 4 or more points and 10 (45.5%) patients were functionally independent (mRS 0-2) at 3 months. In the group of patients with wake-up stroke and with no functional deficit (mRS 0) before the stroke, 9 of 17 patients (52.9%) were functionally independent at 3 months. In a multivariate regression analysis, there was no indication of poorer outcome for patients with wake-up stroke.

Odds Ratio Estimates [95% CI]		
Sex	Male	0.76 [0.36, 1.59]
	Female	
Age	16-49	4.61 [1.34, 15.9]
	50-64	1 [ref]
	65-79	0.64 [0.27, 1.52]
	80-91	0.80 [0.18, 3.62]
NIHSS pre-thrombectomy	0-11	1 [ref]
	12-19	0.34 [0.13, 0.89]
	20-35	0.22 [0.07, 0.69]
ASPECTS pre	0-5	0.25 [0.06, 0.99]
	6-7	0.29 [0.08, 1.01]
	8-9	0.54 [0.17, 1.69]
	10	1 [ref]
Time to groin puncture	Within 3 h	1 [ref]
	3 – 4.5 h	1.60 [0.43, 5.94]
	More than 4.5 h	0.87 [0.24, 3.17]
	In hospital	0.84 [0.18, 3.90]
	Wake up	0.63 [0.13, 3.19]

**Table 2:** Study III: Multivariate regression analysis. Test for good functional outcome, when pre-thrombectomy mRS=0

#### 5.1.4 Severe adverse events

In study II, we found that 8 patients (4.2%), all of who had an occlusion in the anterior circulation, suffered from a symptomatic intracerebral hemorrhage (SICH) according to the SITS-MOST definition. These hemorrhages were located in the infarcted territory (so-called reperfusion hematomas), most of which occurred within a few hours after the procedure. In addition, 3 hemorrhages occurred during the intervention, resulting in a total proportion of SICH of 5.7% in the anterior circulation (4.6% in total). In this study, no SICH was seen in patients above the age of 80 years, and we found no significant associations between the incidence of SICH and sex, age, baseline mRS, pre-interventional NIHSS and ASPECT scores, or time between symptom onset and treatment. The incidence of SICH was lower when stent retrievers were used, compared with non-stent retrievers (mostly the Merci retriever), but the difference was not statistically significant (figure 21). In study III, we found a stepwise increase in risk of SICH with increasing pre-treatment infarct size (measured in ASPECTS), but this increase was not statistically significant. Out of 6 patients with a post-thrombectomy mTICI score of 1, two had a SICH and the P value for heterogeneity was 0.047.



**Figure 21.** Study II: Symptomatic intracranial hemorrhage (SICH) post-thrombectomy, total (237 patients), stent retrievers (151 patients), and non-stent retrievers (mainly Merci) (47 patients).

## 5.2 STUDY IV

A total of 2 138 publications were identified; of those 1 942 publications did not match the eligibility criteria. Out of the remaining 196 abstracts eligible for evaluation, 22 publications were selected for full text evaluation. Of the 22 publications analysed in full text, 11 were not randomized control trials and hence were excluded. Five randomized trials were further excluded since they did not meet the inclusion criteria, in one study (by Miao et al) no patients received IVT,<sup>152</sup> in MR RESCUE less than 50% received IVT,<sup>114</sup> in SYNTHESIS no patients in the intervention group received IVT,<sup>116</sup> and in SWIFT and TREVO 2 intervention with two different devices were compared without any control group receiving IVT.<sup>112,113</sup> The remaining 6 articles met all of the eligibility criteria and were included in the meta-analysis (IMS III, MR CLEAN, ESCAPE, EXTEND-IA, SWIFT-PRIME and REVASCAT).<sup>115,125-129</sup> In total, the 6 trials randomized 1943 patients to either the intervention group (55%) or the control group (45%).

Time from symptom onset to inclusion varied between less than 3 h in the IMS-III trial to less than 12 h in the ESCAPE-trial. In all trials both the control group and the intervention group received IV tPA, if eligible. Time from symptom onset to treatment with IVT varied from less than 3 h in IMS-III to less than 4.5 h in the other trials. Median or mean age varied between 65-71 years of age. Median NIHSS score was 13–18. Imaging of vessel occlusion status was required before inclusion in all trials, except the IMS-III trial. In the IMS-III trial, 284 patients were randomized before CT angiography was allowed in the study. We therefore chose to perform a post hoc analysis including only patients with baseline CT angiography and vessel occlusion from the IMS-III trial.<sup>153</sup> Finally, in total 824 patients were included in the intervention group.

The primary outcome measure, mRS score of 0–2 at 90 days from symptom onset, was

favoured in the intervention group. The proportion of patients with mRS score 0–2 after 90 days was 46% in the intervention group and 28% in the control group. The absolute risk reduction for the intervention group compared to the control group was 19% (95% CI 14% to 23%). Number needed to treat (NNT) for mRS 0–2 in the intervention group was 6 (95% CI 4 to 7). There was a significantly reduced risk of mortality in the intervention group (15%) compared with the control group (20%), with an absolute risk reduction for death of 4% (95% CI 1% to 8%) in the intervention group. Patients receiving IVT alone had a higher probability of mRS 5–6 and death after 3 months; this has not been shown in previous single randomized trials. For mortality alone, the risk reduction was not significant in the second analysis, when the results from IMS III trial were excluded (table 3 and 4).

**Table 3** Outcome 90 days after stroke symptom onset comparing the intervention and control groups\*

Outcome	Endovascular group (n (%))	Control group (n (%))	OR (95% CI)	p Value
mRS 0–2 (functional outcome)	380 (46)	205 (28)	2.21 (1.78 to 2.74)	<0.00001
mRS 0–1 (excellent outcome)	235 (29)	101 (14)	2.46 (1.89 to 3.22)	<0.00001
mRS 0–3	509 (62)	320 (43)	2.15 (1.75 to 2.64)	<0.00001
Mortality	125 (15)	146 (20)	0.73 (0.56 to 0.96)	0.02
Symptomatic intracerebral hemorrhage	41 (5)	34 (5)	1.05 (0.65 to 1.68)	0.85
mRS 5–6	188 (23)	249 (33)	0.58 (0.46 to 0.73)	<0.00001

\*Subgroup from IMS-III with CT angiography verified vessel occlusion.  
IMS-III, Interventional Management of Stroke-III; mRS, modified Rankin Scale score.

**Table 3.** Study IV: Outcome 90 days after stroke symptom onset comparing the intervention and control groups (from IMS III, the subgroup with CT angiography verified vessel occlusion).

**Table 4** Outcome 90 days after stroke symptom onset comparing the intervention and control groups, excluding IMS-III

Outcome	Endovascular group (n (%))	Control group (n (%))	OR (95% CI)	p Value
mRS 0–2 (functional outcome)	295 (47)	170 (26)	2.48 (1.95 to 3.15)	<0.00001
mRS 0–1 (excellent outcome)	172 (27)	83 (13)	2.59 (1.92 to 3.48)	<0.00001
mRS 0–3	400 (63)	275 (42)	2.34 (1.87 to 2.94)	<0.00001
Mortality	97 (15)	122 (19)	0.80 (0.60 to 1.08)	0.14
Symptomatic intracerebral hemorrhage	26 (4)	28 (4)	1.00 (0.58 to 1.71)	0.99
mRS 5–6	139 (22)	217 (33)	0.57 (0.44 to 0.73)	<0.00001

IMS-III, Interventional Management of Stroke-III; mRS, modified Rankin Scale score.

**Table 4.** Study IV: The same outcomes as Table 3, but with the results from the IMS III trial excluded.

### 5.3 STUDY V

During the time period for our computerized database (2009-2011), Riksstroke reported 75 890 stroke treatments for all of Sweden, and of these 65 378 were ischemic stroke. In the ischemic stroke population, 24 125 patients had an NIHSS score registered. After exclusion of patients reported from the Karolinska University Hospital-Solna (since they might have been triaged because of stroke severity) and a few for other reasons, 23 021 patients were included in our study. Among patients arriving primarily (without any pre-hospital triage) to Karolinska, thrombectomy was performed in 6.5% of all stroke-cases, which was 9 times higher than in all of Sweden (0.72%).

At the study time, the most recent Riksstroke data was the annual report from 2013. There the total number of ischemic stroke events was 20 961, and 232 thrombectomies were recorded. The estimated number of potential thrombectomies among these ischemic stroke patients was 1 269, assuming that the NIHSS score distribution was the same as in our material. If the new guidelines for acute ischemic stroke, as executed at Karolinska, had been implemented in all of Sweden, 1 037 (1 269-232) additional thrombectomies would potentially have been carried out. The number of thrombectomies would have been more than 5 times higher (1 269/232).

### 5.4 SUMMARY

To summarize we have found that, in study I, thrombectomy had significant better result compared with other studies on posterior circulation stroke when either IVT or no reperfusion therapy at all was given. Study II showed that mechanical thrombectomy was a safe and effective method to restore blood flow in selected patients suffering from an acute ischemic stroke, and that stent retrievers were more effective in revascularisation than older devices (although not statistically significant in this study). We also found that neither prior treatment with IVT nor high-attained age was significantly associated with risk of symptomatic intracranial hemorrhage. In study III we found that when selecting patients according to our practice, functional outcome after mechanical thrombectomy was as good for those over 80 years of age as for those between 50-64 or 65-79 years of age. In study III, we found no indication of poorer outcome for patients with wake-up stroke. In the meta-analysis, study IV, we found that endovascular treatment combined with IVT led to a higher ratio of patients with an improved clinical outcome than treatment with IVT alone, with an absolute risk reduction of 19% for the intervention group compared with the control group. An estimation of future need for thrombectomy in study V, revealed that the rate of thrombectomies in 2013 might have been more than five times higher in Sweden than the actual rate if the new treatment recommendations had been implemented by then.

## 6 DISCUSSION

### 6.1 GENERAL CONSIDERATIONS

When this project started, endovascular mechanical thrombectomy clearly had promising results in published registries and studies, but there were no large, multicentre, prospective randomized trial comparing mechanical thrombectomy with best medical treatment. As with every other interventional procedure, mechanical thrombectomy obviously also carries a risk for the patient and the question of risk-benefit becomes evident. Because of this, many voices argued for large randomized trials. Others, however, claimed that with the excellent results that were reported for mechanical thrombectomy in properly selected patients, it would indeed be unethical to deny stroke patients this opportunity and thus there was no need for a randomized study.

Our way to address this dilemma was an observational study of our own material. We also planned to compare stroke patients who had been treated with thrombectomy to patients who had either IVT alone or no recanalization therapy. There have been studies comparing results from well-designed observational studies, including control subjects, with randomised controlled trials of the same topic, indicating that the results are remarkably similar independent of study design.<sup>154</sup> When the results from the randomized trials published in the beginning of 2015 were overwhelmingly positive, and confirmed our early study results, we decided to instead conduct a study to estimate the future need of thrombectomies (study V).

The main limitations with the studies included in this thesis are listed below. Study I-III and V (thrombectomy patients) emanate from a single centre, limiting the possibility to generalize the results. Since the studies were not randomized, there are no reference groups treated with best medical care for comparison. The retrospective design with data collected from medical records or registry data made us dependent on the information available in the records, and therefore there are some missing data. We also lack information on patients who we decided not to treat with thrombectomy. The study I cohort is small, limiting the ability for subgroup analysis. In study V there is a difficulty in assessing how many potential thrombectomy candidates would develop a large infarction during transportation to a tertiary centre, thereby disqualifying them from the procedure. Finally, the observational design of the studies is subject to all limitations inherent with this methodology.

Being a single centre study, the presented work also has some advantages, such as access to updated medical records for all patients and a consistency of patient selection and basic treatment techniques. All consecutive thrombectomies performed were included, providing us with useful data of what can be expected outside of a randomized trial. Patients who would have been included in a randomized study are to a large extent included in our material. All patients were included on the basis of radiological verified vessel occlusion, and the use of CTP for patient selection allowed us to also include patients with wake-up stroke. In study V

the availability of data from Riksstroke gave us access to information from a large number of stroke patients from all over Sweden.

## **6.2 STUDY I – POSTERIOR CIRCULATION STROKE**

In study I, we found that with mechanical thrombectomy as the first line treatment for acute basilar occlusion, the proportion of patients who gained functional independence was 57% and for patients without signs of acute infarction before thrombectomy the proportion was 73%. Only 21% died, and among those patients without CT detectable infarcts before treatment, mortality was only 9%.

In a previous meta-analysis of intravenous thrombolysis for basilar artery occlusion a favourable outcome (mRS 0-2) for only 22% was reported, compared with 57% in our study.<sup>142</sup> Mortality was 53% (40 - 70%) for cohorts treated with IVT. The corresponding values for intra-arterial thrombolysis were not superior. In BASICS (a prospective registry study published in Lancet Neurology in 2009), the largest study presented on the treatment of basilar artery occlusion, only 34% of the patients (41 of 121 patients) treated with IVT had a favourable outcome (mRS 2 or less) and 34% of the patients died (41 patients).<sup>140</sup>

Another meta-analysis of reperfusion versus no reperfusion of acute basilar occlusion, including 45 observational studies (n=2056), showed NNT of 3 to decrease death and dependency (defined as mRS >3) and NNT of 2.5 to decrease death alone.<sup>155</sup> In this meta-analysis recanalization achieved with IVT, IAT or thrombectomy were not separated.

There have been several single centre studies published during the last years with good functional outcomes following basilar artery thrombectomy.<sup>143-148</sup> A systematic review of 16 studies, in which basilar artery occlusions were treated with stent retrievers showed a good outcome (mRS 0-2) in 42%, with a recanalization rate of 81%, and a mortality rate of 30%.<sup>149</sup>

The results from study I, supported also by other studies on thrombectomy for basilar artery occlusion, strongly indicate that mechanical thrombectomy is at least as effective in the posterior circulation as in the anterior circulation.

Recruitment is on-going for Basilar Artery International Cooperation Study (BASICS), a randomized trial comparing intra-arterial treatment in addition to best medical management (BMM) with BMM alone (BMM may include IVT). With support of the positive result from randomized trials of anterior circulation stroke, together with the results from our and other single centre studies, ethical considerations raise concerns against randomising patients with basilar occlusion and thereby potentially denying them thrombectomy. An observational study or a registry study could be a more appealing alternative.



### 6.3 STUDY II – REVASCULARIZATION, OUTCOME AND SAFETY

In study II we found that by treating acute occlusions in the large cerebral arteries with mechanical thrombectomy, 50% of all patients obtained independence (mRS 0–2) at follow-up. When restricting the analysis to patients with excellent functional status before stroke onset 54% had gained independence. In our study, performed with a mixture of old and new devices, we achieved TICI 2b-3 in 72% of all cases, but when we used only stent retrievers, mTICI 2b-3 was achieved in 80% compared to 66% when non-stent retrievers were used (no statistically significant difference). We demonstrated that neither prior treatment with IVT nor high-attained age was significantly associated with risk for symptomatic intracranial hemorrhage.

At the time (April 2014) of publication of the results of study II, our study confirmed the results from a retrospective multicentre study by Davalos et al., using the Solitaire device,<sup>111</sup> as well as from the SWIFT-trial<sup>111</sup> and TREVO EU.<sup>110</sup> In study II, the proportion of patients with functional independence three months after stroke was higher in our cohort than in the intervention groups in the three randomized trials, IMS III, MR RESCUE and SYNTHESIS, published in 2013.<sup>114-116</sup>

When the five randomized trials were published in 2015, their results were in line with the results presented in study II.<sup>125-129</sup> The proportion reaching independence three month after thrombectomy varied from 33% to 71% (Table 5). In the control groups (IVT) the proportion varied from 19% to 40%. In our meta-analysis, study IV, mRS 0-2 was reached in 46% in the intervention group and in 28% in the control group. Recanalization (mTICI 2b-3) was achieved in 59% to 88%. Mortality (mRS 6 or death at 3 months) varied in the intervention group from 9 to 18%, compared to 15% in our meta-analysis. In the control group it varied from 8 to 20%.

Although all of these studies are consistent, there are obviously differences in the degree of revascularization as well as good functional outcome at three months. The two trials with the best results are EXTEND-IA and SWIFT-PRIME,<sup>127,128</sup> both of which had shorter time from stroke onset to thrombectomy than the other trials, and also used penumbral imaging for selection. ESCAPE,<sup>126</sup> which had intermediate results, used multiphase CT for collateral imaging for selection. MR CLEAN and REVASCAT had longer times from onset to intervention,<sup>125,129</sup> and used no penumbral or collateral imaging for selection.

The development of new strategies in health care, such as more awareness of the possibilities of performing thrombectomy in acute stroke, increased achievability of rapid referral between hospitals and shorter in-hospital door-to-treatment times, together with the development of stent retrievers has increased the chances of good functional outcome. The differences in revascularisation, good functional outcome and proportion of SICH, although not statistically significant, demonstrated between stent retrievers and old devices in study II, can be seen as a

function of this development; also reflected in the superior results of later randomized trials compared to the inconclusive ones from 2013.

	Study II and III anterior	MR CLEAN	REVASCAT	Escape	EXTEND- IA	SWIFT PRIME	Study IV meta- analysis
Number	192	233	103 (103)	165 (150)	35 (35)	98 (98)	824
Median age	66	66 (66)	66 (67)	71 (70)	69 (70)	66 (65)	65-71
Median NIHSS	16	17 (18)	17 (17)	16 (17)	17 (13)	17 (17)	13-18
Median ASPECTS	8	9 (9)	7 (8)	9 (9)	-	9 (9)	-
TICI 2b-3 [%]	72	59	66	72	86	88	-
mRS 0-2 at 3 months	50	33 (19)	44 (28)	53 (29)	71 (40)	60 (35)	46 (28)
Mortality [%]	14	9 (8)	18 (16)	10 (19)	9 (20)	9 (12)	15 (20)

**Table 5.** Baseline characteristics and outcome of patients with anterior circulation stroke from Study II and III compared with the five randomised trials and with Study IV (meta-analysis). Numbers refer to intervention group, with control group in parenthesis, and are rounded up or down to the nearest integer.

## 6.4 STUDY III – WAKE-UP STROKES AND ELDERLY

In study III, we studied patients with anterior circulation stroke in more detail. The most interesting results were that both patients over 80 years of age as well as patients with wake-up stroke, may experience a favorable outcome after treatment - at least if they were selected according to the presented local Karolinska practice.

In Sweden, patients above the age of 80 years have since 2014 been receiving intravenous thrombolysis according to new guidelines.<sup>156</sup> In many centres they are also considered for thrombectomy, even though they were excluded from some of the randomized trials. The median age in the five randomized trials published 2015 was between 65-71 years. In all those trials patients had to be 18 years old or older. Some of the trials had an upper age limit (80-85) but two of them, MR CLEAN and ESCAPE, did not. We found that when patients were selected according to local Karolinska practice, there were no significant differences in functional outcome after mechanical thrombectomy for those over 80 years of age compared

to those aged 50-64 and 65-79 years. This result is supported also by the results from MR CLEAN and ESCAPE, where treatment effect was also found to remain consistent over the age of 80.



**Figure 22.** Pre and post thrombectomy images of a 90 year old woman who had a NIHSS score 21 at arrival. Left M1 occlusion (left image) was found. Thrombectomy was performed, and the blood supply restored (right image). Her NIHSS score was 0 when she left the hospital.

Time to treatment is of course of great importance for the stroke population in general, even though such factors as extent of collaterals may be as important. Since collateral status and the remaining function on cellular level is impossible to fully ascertain in advance, we must make every minute count in our effort to save brain tissue. The median time from stroke onset to groin puncture varied among the randomized trials from 210-269 min (perhaps less in ESCAPE, not clearly stated), but the inclusion criteria varied even more; in most cases endovascular treatment should be initiated within 6 hours or patients should be treated within 8 hours, but in ESCAPE treatment was to be initiated as late as up to 12 hours after stroke onset.

In study III, we found no statistically significant association between time from symptom onset to groin puncture and functional outcome, suggesting that using perfusion imaging as a part of the selection process might increase the ability to find the patients most likely to benefit from the treatment - even when a long or unknown time has passed between stroke onset and initiation of treatment. Another explanation might be that at least some patients wake up the moment the stroke occurs, implying that the time actually is not “unknown”.<sup>157</sup>

A recent systematic review concluded that there is not sufficient evidence to make recommendations on treatment for patients with wake-up stroke.<sup>158</sup> Wake-up strokes were not included in any of the randomized thrombectomy trials discussed in this thesis, although patients were allowed to start treatment up to 12 hours after stroke onset in ESCAPE, which could allow some patients with wake-up stroke to be included even though not clearly indicated as such. We found that wake up-strokes, and other causes of unknown time from stroke-onset, are a subgroup of patients that would most likely benefit from rapid radiological evaluation for eligibility for thrombectomy. The findings highlight the importance of further studies for this group of patients, and suggest that future studies on mechanical thrombectomy should also include patients with wake-up stroke.

Encouragingly, there is currently one ongoing study concerning thrombectomy in wake-up stroke, Trevo and Medical Management Versus Medical management Alone in Wake Up and Late Presenting Strokes (DAWN), still recruiting patients.<sup>159</sup> In both Europe and Japan, studies involving IVT and wake-up stroke are ongoing.<sup>160,161</sup>

## **6.5 STUDY IV – META-ANALYSIS**

The aim of this meta-analysis was to evaluate the role of endovascular treatment in acute ischemic stroke. The study included six randomized controlled trials. The results showed that endovascular treatment, including mechanical thrombectomy, leads to a higher proportion of patients with an improved clinical outcome after 3 months from stroke onset compared with the control group receiving IVT alone. Patients receiving IVT alone had a higher probability of mRS 5–6 at 3 months, which has not been shown in previous single randomized trials.

Since our study was published, other meta-analyses have confirmed the conclusion that treatment with thrombectomy is associated with better functional outcome than IVT alone, although with variable rates depending on included studies.<sup>132-135</sup> In April 2016, the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration published a meta-analysis consisting of individual patient data from the five randomized trials published 2015.<sup>162</sup> The number needed to treat with endovascular thrombectomy to reduce disability by at least one level on mRS for one patient was 2.6. With individual patient data, subgroup analysis could be made, showing that the results were valid also for patients aged 80 years or older, for those randomized more than 300 minutes after symptom onset, and for those not eligible for IVT.<sup>162</sup> These results also confirm the results from study II (patients not receiving IVT) and study III (patients above 80 years of age).

## 6.6 STUDY V – ESTIMATION OF INCREASING DEMAND

In study V, by comparing our results to patients from Riksstroke, we showed that the number of thrombectomies in 2013 might have been more than five times higher than the actual number if the practice used at the Karolinska University Hospital – a practice similar to the new guidelines - had been extrapolated to all of Sweden. The estimated potential demand for thrombectomies was more than 1200 patients compared to the 232 reported that year. Although it is difficult to assess how many potential thrombectomy candidates would develop a large infarct during transportation to a tertiary center, the study still shows that there will be a substantial increase in demand for thrombectomy in the near future. To provide more equal stroke care for patients living in different regions there is a need for a general policy. Different strategies will probably have to be implemented and combined, including improved and extended networks with access to rapid transportation, refined pre-hospital triaging with suitable patients with a high likelihood of harboring large artery occlusion transported directly to a comprehensive stroke center,<sup>163</sup> and increased education and increased capacity to do interventional procedures, i.e. need for additional neurointerventionists.

Studies have recently been made of costs and quality of life, in which patients receiving IVT and thrombectomy have been compared to patients receiving IVT alone.<sup>164-166</sup> In Sweden, the Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket, TLV) on behalf of the Swedish government conducted an investigation presented in the end of 2015, that showed that IVT plus thrombectomy is with high probability a cost effective treatment option for acute severe ischemic stroke.<sup>167</sup> Part 2 of this investigation is to be presented to the government in December 2016, but the report was published in June 2016.<sup>168</sup> The last report investigated the possibilities and costs for transportation of patients from remote areas in Sweden to five (the situation today), six or seven (all University Hospitals of Sweden) tertiary centers where thrombectomy could be performed, depending on availability of neurointervention. The possibility of transportation with ambulances or helicopters was discussed. The conclusion was that thrombectomy in Sweden was cost effective even when helicopter transportation was needed, and the availability of neurointervention in more centers than currently (six or seven compared with five) would decrease the cost substantially. The possibility of rapid access to a center able to perform mechanical thrombectomy is essential; an analysis from data from the SWIFT-PRIME trial showed that with reperfusion later than 2.5 hours from symptom onset every subsequent hour decreased the possibility of functional independence with 20%.<sup>169</sup> In larger cities one could also consider pre-hospital triage of patients with moderate to severe stroke, directing ambulances to hospitals able to perform thrombectomy. In mild to moderate stroke, the chance of good effect from IVT is higher, indicating that the possibility of helping these patients might be better at the closest hospital. This is a question in need of further evaluation.

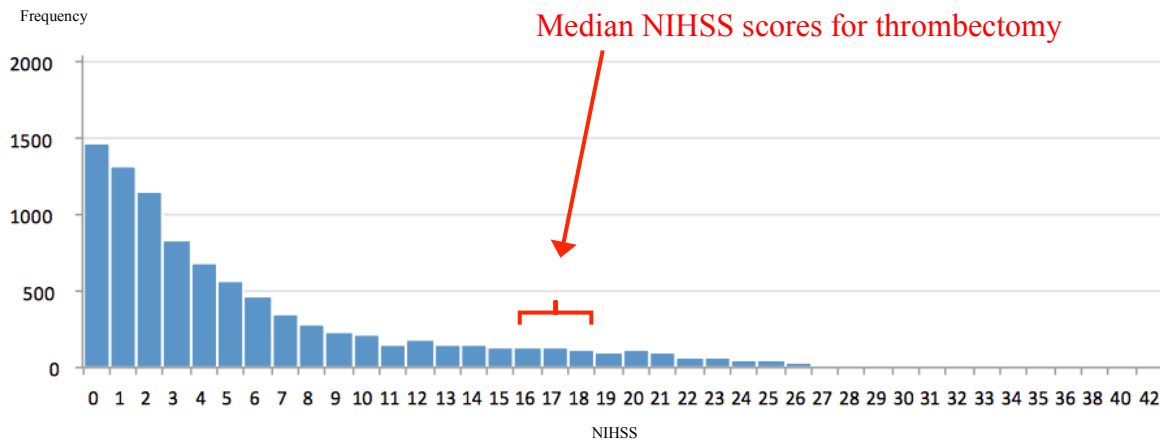
Recently, “European recommendations on organization of interventional care in acute stroke (EROICAS)” was published.<sup>170</sup> Six European scientific societies (in alphabetical order:

European Academy of Neurology (EAN), European Association of Neurosurgical Societies (EANS), European Society of Emergency Medicine (EuSEM), ESMINT, ESNR, and ESO), have agreed on this consensus document regarding organization of interventional care in acute stroke. There are recommendations for many different steps during the care, for example which patients should be treated, by whom and how, preclinical and clinical requirements (discussing the question of direct transfer), and care after treatment. Notably, time from stroke onset to groin puncture should preferably be within 6 hours, and no later than 12 hours. No upper age limit and no limit in NIHSS score are recommended for thrombectomy and eligible patients should have a pre-stroke mRS score of 0-1.

In study V, we show that the main challenge now is to fully implement mechanical thrombectomy in clinical practice and to provide access to this treatment not only to patients living in the proximity of university hospitals, but to all patients in Sweden

## **6.7 WHICH STROKE PATIENTS SHOULD BE CONSIDERED FOR MECHANICAL THROMBECTOMY?**

There were different inclusion criteria in the randomized trials, for example in MR CLEAN patients could be included with milder symptoms (from NIHSS score 2) than in the other trials. This likely did not affect the result in any substantial way since the median NIHSS score is fairly similar in all these trials. In EXTEND-IA's control group the median NIHSS score differs by being clearly lower than the others; 13 compared to 16-18 in the others. This might in part explain the superior results for the control group in EXTEND-IA (mRS 0-2 in 40 %). The consistent high median NIHSS score among the other trials is interesting since it shows that patients with large vessel occlusions, eligible for thrombectomy, usually have severe symptoms. This is in line with the median score of 16 in our material, in which patient selection was not restricted to a study protocol. In Riksstroke annual report 2014 the NIHSS score was reported in 48% of stroke patients in all of Sweden.<sup>4</sup> Among them the median NIHSS score was 3. There is obviously a large difference, showing that most patients with stroke will not be eligible for thrombectomy. Our results from study III demonstrate that larger groups of patients might benefit from thrombectomy, including wake-up strokes, but this would probably not affect the median NIHSS score in any substantial way.



**Figure 23.** NIHSS score at arrival to hospital, for stroke patients registered in Riksstroke 2014.<sup>4</sup> In red the median NIHSS scores for thrombectomy patients (according to study II and several studies in table 5). (*Image is reprinted with permission from Riksstroke, figures and text in red are added by the author of this thesis*)

It is also worth noting the median ASPECTS, which is 9 in both the intervention group and the control group in three of the trials. In REVASCAT the median ASPECTS was 7 and 8, respectively, and in our study it was 8, indicating that a larger manifest infarction already existed before treatment and therefore making a complete recovery more unlikely in these studies compared to the others. It also shows that most often patients with no, or only minor manifest infarcts are selected for thrombectomy. In study III, where we discussed factors influencing the results, we found that we had a tendency to treat young patients (below 50 years of age) with larger already manifest infarctions. In that age group 69% had an ASPECTS of 7 or below, but they still did significantly better at follow-up, with an odds ratio of 4.61 (1.34-15.9) for good functional outcome (mRS 0-2 at three months) compared to the age group 50-64. This might indicate a difference in potential for rehabilitation between age groups, and perhaps the need for age-differentiated selection criteria.

Most studies, including ours, have focused on independence (mRS 0-2) as outcome measure. By now, the benefit of thrombectomy in large artery occlusion in the anterior circulation, as described above, is established. One can argue that the time has come to study the effect of thrombectomy on more severe stroke, with larger already manifest infarctions, for example ASPECTS <7 or even <5. If death or the most severe outcome (mRS 5-6) could be avoided with thrombectomy, a result of mRS 3 or even mRS 4 could be considered as good outcome. Or is the risk of a reperfusion hemorrhage too high, or the benefit too low? Is there a difference between age groups (considering the good results seen in study III for patients below 50 years of age and with low ASPECTS)? A randomized trial including this group of patients could be of great value.

## 7 CONCLUSION AND FUTURE

Our studies have showed that mechanical thrombectomy is a safe and effective treatment option for stroke caused by large artery occlusion in the anterior circulation, and that patients treated with mechanical thrombectomy in conjunction with IVT showed improved functional outcome and lower mortality than patients treated with IVT alone. The patients selected for treatment with thrombectomy usually suffer from a moderate to severe stroke, with a median NIHSS score around 16-18, have a verified occlusion of a large artery and absence of large manifest infarction, together indicating that there is a select group, and not all stroke patients, that will be eligible for thrombectomy.

We have also shown that thrombectomy is safe and effective in the posterior circulation, with results surpassing those published for IVT. This, together with already proven good results for thrombectomy in the anterior circulation, makes the need for randomized trials in the posterior circulation ethically questionable. The efficacy and safety could be further investigated in observational or registry studies. For example, in Sweden all thrombectomies performed since 2013 are registered in a National quality registry, EndoVaskulär behandling av Akut Stroke (EVAS), which will enable nationwide research concerning thrombectomies in Sweden. The first annual report, from 2014, is available online.<sup>171</sup> An international registry where thrombectomy patients can also be registered is the SITS Thrombectomy Register.<sup>172</sup> These registries provide excellent means to study mechanical thrombectomy in basilar artery occlusion without jeopardizing the health and lives of the patients, as might be the case in a randomized clinical trial.

Patients aged above 80 years old as well as patients with wake-up stroke may experience a favourable outcome after thrombectomy, and should not be excluded from treatment. Future studies could well include patients with unknown time of symptom onset. It could also be interesting to consider age differentiated selection criteria, as well as study results for patients with lower pre-treatment ASPECTS.

Other questions that need to be addressed, and that have not previously been discussed in this thesis, are for example whether to use conscious sedation or general anaesthesia, and how to approach more distal occlusions. Neuroprotective therapies might present a way to gain time for referral patients to reach a tertiary centre. Other areas where development can be expected are new intravenous thrombolytic drugs or adjuvant therapies, prevention of reperfusion injury and improvement of endovascular devices.<sup>173</sup>

When the new treatment recommendations for large artery occlusion are fully implemented, an increased demand for mechanical thrombectomy can be expected. There is a need for policymakers, hospital administrators, and healthcare professionals to prepare for this increasing demand. This implies the need for general policies to provide as equal stroke care



as possible nationwide to all patients. In Sweden, the report from TLV on thrombectomy in acute severe ischemic stroke provides a foundation for that. In larger cities one could also consider pre-hospital triage of patients with moderate to severe stroke, directing ambulances to hospitals able to perform thrombectomy. In mild to moderate stroke, the likelihood of benefit from IVT is higher, indicating that the possibility of helping these patients might be better at the closest hospital. This is a question in need of further evaluation.

Not only is there an urgent need for training of new neurointerventionists experienced enough to safely perform thrombectomy, but also for increased education of neurologists, stroke physicians, emergency physicians, nurses, paramedics and all other healthcare providers involved in patients with acute ischemic stroke. This is needed all over the country, not only at university hospitals, in order to provide as equal opportunities as possible, independent of who takes care of the patient first. An increased public awareness is also needed, in order to reduce the time from onset of symptoms to arrival to hospital.

There are still many question to answer and details to study, but the advantages of thrombectomy in ischemic stroke caused by an acute large cerebral artery occlusion have been well proven. Our main challenge now is to fully implement the technique in clinical practice and to provide access to mechanical thrombectomy not only to patients living in the proximity of university hospitals, but to all patients in Sweden.



## 8 ACKNOWLEDGEMENTS

There are many to whom I would like to express my sincere gratitude for support and contribution to this thesis. In particular:

**Magnus Kaijser**, my main supervisor and current chief of the neuroradiology department. Your encouragement and belief in my capability have been invaluable for the completion of this thesis. Your expertise in epidemiology and statistics enabled much of this work. Thank you for all the fun discussions while doing the analyses, and for showing me the joy of epidemiological research!

**Tommy Andersson**, my main supervisor during the first years and later co-supervisor (after moving abroad), and also former head of neurointervention. Your expertise in the field of neurointervention, and mechanical thrombectomy in particular, has been of great importance. Most of all thanks for your clinical supervision, in teaching me how best to perform a neurointerventional procedure.

**Staffan Holmin** and **Niaz Ahmed**, my co-supervisors. It has been a pleasure to collaborate with you! Your attention to details and your scientific advice have been most useful.

**Nils Wahlgren**, co-author to four of my articles, with deep knowledge in the field of stroke. Although not formally my supervisor, you have provided invaluable support and scientific guidance.

**Anna Falk-Delgado**, **Alberto Falk-Delgado** and **Jian Fransén**, co-authors of the meta-analysis. It was a pleasure to work with you. Your speed and ambition are a real inspiration!

**Anne Zachau**, my mentor, for encouraging me to prioritize other essential parts in life, such as reading fiction and novels.

**Olof Flodmark**, former chief of the neuroradiology department, for encouragement and belief in me. Thank you for giving me the opportunity to join first the neuroradiology department and later the neurointervention group, and for your support during the work on this thesis. Most of all, thank you for creating a positive and inspiring work environment at the department of neuroradiology.

**Michael Söderman**, current head of neurointervention, for great support in everyday work and constant encouragement. I really appreciated your willingness to give a helping hand when on-call work and research work were in conflict!

**Åke Holmberg**, research nurse, for help with setting up the database and lots of other practical things. Most of all for always being helpful and providing me with data (if possible ten minutes ago!).

**Marcus Ohlsson**, colleague in neurointervention, for friendship and encouragement.

All of my colleagues, doctors and nurses, at the angiosuite: **Patrick Brouwer, Johanna Doshé, Dick Sonnell, Hans Westerholm, Ulrika Nilsson, Yvonne Olejnik, Danilo Olivares, Lena Bonna, Johanna Åkerblom**, and **Homayoun Farokhi** (who worked with us when I gathered my material). It is so fun and rewarding to work with all of you!

**Håkan Almqvist**, head of the CT-section, for many interesting discussions and for sharing experiences during the PhD-time. Thank you also for good collaboration in setting up a effective examination of acute stroke patients together with your team; especially **Erik Jensen, Hanne Witt, Britt-Inger Sohlin, Johanna Rouvinen** and **Behnam Eskandari** (who has now joined us in the neurointervention group!).

**Per Grane**, my first clinical supervisor in neuroradiology, for teaching me so much! It has been a joy to have the opportunity to work together with you in spinal intervention.

All personnel at the neuroradiology department for the fantastic work including performing and evaluating CT, CT angiography and CT perfusion day as well as night, every day of the year!

The colleagues from the neurology department, especially the stroke-team; **Christina Sjöstrand, Magnus Thorén, Anna Steinberg, Erik Lundström, Michael Mazya, Tiago Moreira, Charith Cooray, Albert Hietala**, and the team of dedicated stroke nurses. Also **Mia von Euler** and **Nikolaos Kostulas**, former colleagues. The collaboration with you is the foundation for the excellence of our stroke-unit.

Doctors and nurses from the department of neuroanesthesia, for valuable collaboration, taking care of the patients so that we can perform the thrombectomies. Thrombectomy needs teamwork, and we could not do without you.

All doctors, nurses and other personnel, taking part in everyday care of stroke patients, at various departments at Karolinska, at all our referral hospitals and in the pre hospital care. The effort you make to speed up the process and use your skills to improve the outcome for every single patient is what really makes the difference!

**The Riksstroke Collaboration**, for collecting and sharing comprehensive data on stroke patients in Sweden.

**Heather Martin**, colleague from diagnostic neuroradiology, for the effort of proofreading.

**Elisabeth Rooth**, my dear friend since first semester in medical school, who also shares the interest for stroke. You have always set a good example, and showed me that it is possible to balance work with family life and leisure time. I highly appreciate your willingness to listen to me, and your encouragement when my writing is too slow or when time is scarce. **Mats** and **Laura Nordlund**, for true supportive friendship and willingness to share your expertise!

My parents-in-law, **Ulf Söderqvist** and **Cecilia Busck Söderqvist**, for their care and support, and for, together with **Peter, Eva, Mimmi, Alma** and **Erik Busck**, giving me the joy of having a large family!

My mother and father, **Anita** and **Harald Kuntze**, for their continuous support and for their unconditional love and belief in me! Without the enormous amount of help from my mother, who has taken care of our children (and of me and Jesper), it would never have been possible for me to work on this thesis and combine it with clinical work and on-calls!

My three wonderful sons, **Jacob, Linus** and **Martin**! You are the best!

and finally, **Jesper**, my husband and best friend, for love and support and for always being there for me. The best times in life are when I am together with you.



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